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# Command Operations Report

This report is **required** by commands listed in **SNDL Parts 1 & 2** and all operational **Task Forces, Groups and Units** temporarily established to meet operational requirements.

The report format is divided into six sections: Command Data, Commander's Assessment, Chronology and Narrative, Supporting Reports, Published Documents, and Photographs. Required information is identified in specific sections of the form. Instructions on submitting this form and the required attachments are at the end.

## 1. Command Data

Name of your Command or Organization: Naval Medical Resarch Center (NMRC)

Unit Identification Code (UIC), per the SNDL: 32398

Name and Rank of Commander/Commanding Officer/Officer in Charge:

Last: Daniel First: John M.I.: C Rank: CAPT

Date Assumed Command (date format YYYY-MM-DD): 2006-10-27

Mission/Command Employment/Area of Operations: Medical Research

Permanent Location (Home Port for deployable units): Silver Spring, Maryland

Immediate Superior In Command:

Operational: Naval Medical Support Command

Administrative: Naval Medical Support Command

Identify your assigned Task Force/Group/Unit name(s) and mission(s). Include OPLAN(s) and or named operations you participated in during Task Force assignment (if applicable): N/A

Name(s) of Forces, Commands, Ships, Squadrons or Units assigned or under your operational control (if applicable):
Naval Health Research Center (NHRC)
Naval Institute for Dental and Biomedical Research (NIDBR)
Naval Aerospace Medical Research Laboratory (NAMRL)
Naval Submarine Medical Research Laboratory (NSMRL)
Naval Health Research Center Detachment, Directed Energy Bioeffects Laboratory (DEBL)
Naval Health Research Center, Environmental Health Effects Laboratory (EHEL)
Naval Medical Research Unit 3 (NAMRU-3) Cairo, Egypt
Naval Medical Research Unit 2 (NAMRU-2) Jakarta, Indonesia

Type and number of Aircraft Assigned and Tail Codes, if applicable: N/A

Commands, Detachments or Units deployed on board or stationed aboard as tenant activities (as applicable): Naval Medical Research Center Detachment (NMRCD) Lima, Peru

Number of Personnel Assigned:

Officers: 41 Enlisted: 14 Civilian: GS: 76 Contractors: 195

Command Point of Contact (required entry, complete in full):

Name (Rank, First Name, Middle Initial, Last Name): CAPT Vincent DeInnocentiis
Job Title/Office Code: Executive Officer /09
E-mail (both classified and unclassified, if available): DeInnocentiisV@nmrc.navy.mil
Phone number(s): 301-319-7402
Command Mailing Address: 503 Robert Grant Avenue, Silver Spring, Maryland 20910

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## 2. Commander's Assessment

The Commander's Assessment briefly tells the story of the command's role in national defense and should highlight any general and specific lessons-learned. It should contain the commander's commentary, insights and reflections on the unit's activities. Attention should be directed to significant issues impacting training, operations and mission accomplishment during the reporting period. Descriptions of circumstances and sequence of events leading to major command decisions and results of those decisions are particularly desired. Also desired are accounts of specific contributions of individuals in the command to mission accomplishment. For units engaged in or directly supporting combat, significant wartime or peacetime operations (named operations, non-combat evacuation operations, disaster relief or other humanitarian operations, etc.) or major exercises, particular attention should be given to the commander's estimate of the situation, records of discussions and decisions, descriptions of circumstances and sequence of events leading to operational decisions and results of those decisions. For a unit returning from deployment or participating in a single operation this can normally be a single assessment. For higher-echelon commands or units engaging in multiple operations, a separate assessment for each operation in addition to an overall assessment may be appropriate.

The Naval Medical Research Center (NMRC) is a premier research organization committed to enhancing, promoting, and applying basic and applied biomedical research in the areas of infectious diseases, biological defense, combat casualty care, environmental medicine, diving and bone marrow. The mission of the Naval Medical Research Center (NMRC) is to conduct research, development, tests and evaluations to enhance the health, safety, and readiness of Navy and Marine Corps personnel in the effective performance of peacetime and contingency missions, and to perform such other functions or tasks as may be directed by a higher authority.

Capabilities and Core Competencies

· Basic and applied research, product development, testing, and evaluation in areas of military importance including infectious diseases, combat casualty care, bone marrow investigations, and biological defense.
· Worldwide infectious disease surveillance, particularly in emerging or re-emerging infectious diseases of military importance.
· Cadre of scientific leadership and technical expertise.
· Technology watch for medical products of potential use by the military.
· Scientific advisors and medical consultants for Navy Medicine and the military Operational Commanders.
· Forward deployable diagnostic and consultant capabilities in infectious disease, bone marrow, and biological defense to support Operational Commanders.
· Worldwide research laboratory infrastructure and support capabilities.

As we move into the 21st century, we face not only the medical issues associated with conventional warfare, but the potential use of weapons of mass destruction and terrorism against our military forces and our citizens. The overwhelming superiority of our defense infrastructure, where billions of dollars are invested, is vulnerable to the threat to use inexpensive asymmetric weapons of mass destruction against us. As such, our research at NMRC is focusing on finding solutions both to conventional medical problems on the battlefield such as bleeding, and to non-conventional weapons such as thermobaric blast, biological agents, or radiation. Research is being conducted in the fields of Infectious Diseases, Biological Warfare Defense, Dental Research, and Combat Casualty Care.

As a continuation from the last reporting period, NMRC was re-organized to an Echelon 5 Command and gained new subordinate laboratories as a part of the re-organization. Our Immediate Superior In Command is the Naval Medical Support Command.

Our overseas laboratories play an instrumental role in the worldwide monitoring of new emerging infectious diseases such as Avian Influenza, and SARS that threatens both deployed forces and the world. The threatened deliberate use of biological agents as weapons in the future may require infectious diseases to be classified as battlefield related, and will be extremely serious to the unprepared.

During the reporting period, NMRC research has continued to unfold with ever increasing success and unquestioned high acclaim at NMRC itself, in other Navy laboratories, and in partnership with other federal agencies. Non-federal collaborations are promoted

through an extremely successful and active technology transfer program that includes various cooperative research and development agreements (CRADAs) with universities and private industries. Navy-supported medical research efforts have influenced the civilian practice of medicine, assisted the Ministries of Health in developing nations, and provided technology for other federal initiatives.

## 3. Chronology and Narrative

Chronology should include dates of movements; local operations and training; exercises and operations (define acronyms and purpose of exercise or operation); installation of new weapons systems or changes; major physical changes to facilities, ship or aircraft; Class A or B mishaps; port visits; unit awards received; reserve augmentation; and other significant operational or administrative events.

Research Services Directorate (02)

Clinical Diagnostics Laboratory (CDLD)

For the calendar year 2006, RSD's CDLD went through a major shift in both personnel and function. The loss of all except one military technician assigned to CDLD was accompanied by a switch in technology used in Cytomegalovirus (CMV) testing, the primary function of the lab in support of the DoD Marrow Donor Program. The sample load for CMV gradually diminished and testing was closed out in favor of a non-invasive saliva-based test. Attempts to distribute remaining CMV reagent and test kits to area hospitals and laboratories were unsuccessful and approximately 100 reagent kits were left unused and allowed to expire. The leased Abbott Axsym analyzer was made available for use for testing other analytes for the remainder of the year but will soon be returned to Abbott Diagnostics Corp since the laboratory is now unable to justify sample volume required to keep the instrument.

The only enlisted CDLD staff left was also assigned the duty as the Command Senior Enlisted Advisor.

Office of Technology Transfer (OTT)

Cooperative Research and Development Agreements (CRADAs)
NMRC Laboratories

During 2006, forty-three (43) CRADAs were negotiated for NMRC and its subordinate labs, bringing in a total of five million, five hundred and sixteen thousand, one hundred and thirty-six dollars ($5,516,136).

Naval Medical Centers

During 2006, fifty (50) CRADAs were negotiated for the NMCs bringing in a total of six million, one hundred and fifty-four thousand, eight hundred and twelve dollars ($6,154,812) in CRADA funds.

Patents

- 6 patents have issued to date in FY06
- 40 Patent applications have been filed to date in FY06 (12 provisionals, 18 non-provisionals and 10 PCT applications)
- 3 Patent License Agreement have been signed in FY06
- 9 Patent License Agreements are in final stages of negotiations

Quality Indicators
- Two FLC Excellence in Technology Transfer awards in 2005
- One FLC Excellence in Technology Transfer award in 2006
"Treatment of Noise-Induced Hearing Loss Through Biologic Mechanisms"
Laboratory: Naval Medical Center San Diego (NMCSD)

- One Southeast Region FLC Excellence in Technology Transfer award in 2006
"Reduced Oxygen Breathing Device"
Laboratory: Naval Aerospace Medical Research Laboratory

Office of Intellectual Property (OIP)

- December 2005: Legal Office undertakes the RESUS project and loses Phil Ketner, one of two attorneys. RESUS becomes almost 70% of the workload with instructions for that project to take priority over other issues.
- October 2006: Issues regarding international agreements with NAMRU-2 are introduced.
- October 2006: Ms Ning Yang is hired to replace Phil Ketner.

Significant Issue:
The legal department provided significant support to the Restore Effective Survival in Shock (RESUS) program in developing the legal issues such as business transaction structure, contracts issues, legal liability and the pursuit of outside counsel. While the legal department has acquired significant experience in the area of regulatory affairs, there is still a significant gap in expertise regarding regulatory affairs and knowledge of Food and Drug Administration (FDA) procedures. The command obtained permission in February 07 to acquire outside counsel to address the legal and regulatory affairs associated with the RESUS project. It has become clear, however, that other matters requiring knowledge of regulatory affairs matters will increase with time.
Lessons Learned:

*Quickly obtain outside regulatory counsel at the when it becomes apparent that the expertise does not exist within the BUMED claimancy or Navy.
*Obtain regulatory counsel at the initiation of the regulatory matter, ie. before pre-IND conferences, if applicable.

*Provide training on regulatory affairs and human subjects protection to legal personnel to increase expertise, ie. attending PRIMR conferences, obtaining Regulatory Affairs Certification (RAC), participating in IRB meetings.
Contributions to Mission Accomplishments:

The legal department participated in almost every briefing of the senior leadership at BUMED, ONR and at the Office of General Counsel to provide an understanding of the legal issues and to make appropriate recommendations regarding the conduct of the study and to obtain outside counsel. The department also participated in numerous regulatory meetings, including a Blood Products Advisory Committee Meeting and represented NMRC and the RESUS team before FDA Counsel and Biopure Counsel regarding the conduct of the BPAC. The legal department assisted in the development of an agreement between FDA, NMRC and Biopure that resulted in the BPAC being able to be held in a public setting. The legal department's representation of NMRC also resulted in a number of unfavorable FDA procedural decisions to be reversed during discussions with FDA Counsel and the Office of Blood Research and Review (OBRR).

Significant Issue:
The legal department provided significant support to the development of Intellectual Property provisions for an Indonesian Country-to-Country Agreement that would ensure the continued presence of NAMRU-2 in Indonesia. Moreover, the agreement would provide the continued ability to receive infectious disease samples from the Indonesian Ministry of Health. The Indonesian Government is currently demanding that they own not only biological samples within Indonesian borders but that they own intellectual property that results from those samples without regard to any intellectual contribution.

Lessons Learned:

The Indonesian agreement highlights the increasing awareness of third world countries in intellectual property and the potential value they represent. Indonesia has demanded some share of the profits and royalty streams obtained by pharmaceutical companies from the biological samples used to produce vaccines. We proposed an IP solution that would solve the problem of biological materials and IP in Indonesia but it may not have any ultimate authority to be executed. Accordingly, we must educate the Indonesians and other third world countries on the vaccine production process. In some cases, we may have to lobby for additional authority to negotiate IP rights with foreign countries if it is in the national interest to do so. We may need to also advocate for foreign aid in appropriate circumstances or risk losing our diagnostic reference laboratories and their capability to perform surveillance. Other countries are likely to learn from the situation in Indonesia and to seek similar benefits. We believe a comprehensive strategy should be developed.

Significant Issue:

A significant population of the NMRC workforce is composed of contractors and/or Intergovernmental Personnel Act (IPA) employees. While IPAs are treated as government employees for many purposes such as assignment of IP rights and tort liability, many IPA assignments are ending. Under new rules regarding the assignment

and extension of IPA's, we are seeing a decrease in IPA's, resulting in personnel who are contractors only. These contractors perform research alongside our government investigators. This presents IP, ethical and fiscal issues that must be considered in every aspect of decision-making within the Command.

- Lessons Learned

The legal department recommended guidance that was provided command-wide that contractors should not be principal investigators to avoid ethical and fiscal issues such as contractors serving in inherently governmental positions that made fiscal decisions or involved supervising governmental employees since contractor employees are still employed by the contractor notwithstanding that their duty station is at NMRC, a government laboratory. The IPA program and the use of contractors should not be used to the extent possible as a temporary measure. These tools were never meant to supplant the Personnel System provided under OPM rules. Where contractors are still present, we recommend a government presence to provide the best opportunity for government inventorship and ownership of any resulting IP.

We also recommend use of contractors that voluntarily waive IP rights in subject inventions arising out of a FAR contract. By waiving rights we mean that the contractor agrees to assign such rights back to the government. The Army has indicated that it is prepared to use an exception to the Bayh-Dole law to require contractors to assign IP back to the government in certain situations. We are investigating the appropriateness of such a tactic for recommendation to the Navy IP Counsel.

Significant Issue:

Lack of organic contracting and grants support for the command has been a major concern for years. After ONR discontinued it's grants and cooperative agreement support, the command lost a valuable tool necessary in the conduct and support of medical research. We subsequently established a grants and cooperative agreement capability with GOVWORKS, an agency of the Department of the Interior. That practice was discontinued after concerns grew that non-DOD agencies were not equipped to provide such services according to the DOD Grants and Agreement Regulation (DODGARS) and discovering the wide variations in agency rules and practices. Having the ability to provide funding using the appropriate instrument is critical in conducting ethically and legally appropriate research.

- Lessons Learned

Non-DOD activities charge administrative fees needed for their continued support but may not pay adequate attention to DOD requirements. Accordingly, the legal department has been a strong advocate that all BUMED activities must have an organic contracting/procurement and grants capability with the associated legal support to provide legal review. The legal department has been instrumental in initiating the effort to obtain support from NAVMEDLOGCOM and its legal support arm and coordinating the data to support that effort.

Organizational Structure

The legal department provided legal support despite operating at below full strength for most of the year. The legal department consisted of one OGC Attorney and one O-6 Microbiologist serving as technical advisor that wrote the patent applications until October 06. We added one junior OGC Attorney in October and hope to add a third Attorney in the upcoming months. Most field activities have 3-4 general attorneys and some have as many as 8-10 patent attorneys.

The Office of Research Administration
Mission: To support the responsible conduct of research through proactive education, policy development, standards and continuous quality improvement in the areas related to human subject protections, grants administration and library services.
In FY06, the Office of Research Administration (ORA) accomplished the following:

- Brought the Office into Compliance by handling a backlog of human subject research materials.
- Hired a range of staff
    - Hired a Compliance Officer – Kimberly T. Gray
    - Hired a Publications Coordinator – Gabriel Hansborough
    - Hired an Information Technology Specialist – Joseph Malone
    - Hired a Research Coordinator – Jon Fletcher
- Assisted NMRCD is obtaining its own IRB and a complete update to its DOD Navy Assurance.
- Assisted NAMRU-2, NAMRU-3 and NIDBR in renewing their DOD Navy Assurances
- Successfully passed the Medical Inspector General Inspection
- Terri Brantley was named Senior Civilian of the Year 2006

Combat Casualty Care Directorate (03)

Major project: RESUS: Restore Effective Survival in Shock – A pivotal, randomized, controlled, and single-blinded trial of the hemoglobin based oxygen carrier (HBOC), bovine polymerized hemoglobin (HBOC-201), for the pre-hospital resuscitation of patients with severe hemorrhagic shock

Description:

The RESUS effort was initiated in FY03 to conduct a Phase III human clinical trial of hemoglobin-based oxygen carriers (HBOC) for use in life threatening trauma. The blood substitute, HBOC-201, manufactured by Biopure Corporation (Cambridge, MA), is a bovine-source polymerized hemoglobin oxygen-carrying low volume resuscitative fluid

that is universally compatible (no blood banking needed) and has been tested in phase I-III clinical trials in over 700 perioperative patients. A successful outcome of the Phase III

trial could lead to the deployment of HBOC-201 for battlefield use. HBOCs are stable at room temperature and have a two- to three-year shelf life. Deploying HBOCs will reduce the logistical burden involved in using blood products requiring refrigeration and the high costs associated with maintaining inventories of perishable blood products.

Milestones:
Significant RESUS project milestones were completed during 2006. However, the FDA Investigational New Drug (IND) application continues to be on Clinical Hold.

- 14 Apr 06 – Teleconference with the FDA regarding the Clinical Hold issues in the 02 Mar 06 FDA Clinical Hold letter.
- Determined that a Blood Products Advisory Committee (BPAC) meeting would be necessary to address the FDA's concerns/questions regarding the Clinical Hold issues.
- Preparation for 14 July 06 BPAC meeting
- NMRC submitted to the FDA NMRC's Briefing Book
- NMRC recruited numerous consultants to assist in NMRC's preparation of the BPAC meeting presentation.
- NMRC organized numerous preparatory meetings with RESUS Advisory Board members (i.e., experts in the field of trauma medicine, emergency medicine, and bioethics), corporate partner and consultants.
- NMRC prepared list of speakers and meeting presentation materials for the BPAC meeting presentation (i.e., PowerPoint presentations and slides).
- NMRC participated in numerous teleconference meetings and correspondence with FDA in preparation for the BPAC meeting.
- NMRC submitted a written request for the FDA to include ad hoc BPAC members who would be knowledgeable in trauma medicine and cardiac physiology.
- NMRC prepared for and hosted rehearsal meetings in preparation for the BPAC meeting.
- BPAC meeting was canceled due to a lawsuit, on the eve of the meeting, from a private citizen's group that objected to the meeting being closed to the public.
- 14 Aug 06 - NMRC submitted a Complete Response letter to the FDA
- 22 Sept 06 – FDA letter to notify NMRC that the RESUS study continues on Clinical Hold.
- 04 Oct 06 – Type 'A' and 'C' meeting with the FDA to discuss clinical Clinical Hold issues.
- Safety data discrepancies between FDA and corporate sponsor regarding previous HBOC-201 clinical trials have been resolved.
- 10 Oct 06 – Type 'A' meeting with the FDA to discuss pre-clinical Clinical Hold issues.
- BPAC meeting rescheduled by the FDA for 14 Dec 06 to include an open public hearing session.
- Preparation for 14 Dec 06 BPAC meeting (as above for 14 July meeting)

- NMRC and corporate sponsor recruited participants for the open public hearing session of the BPAC meeting and for submission to the FDA written comments in support of emergency trauma medicine and the RESUS study.
- 14 Dec 06 - FDA BPAC meeting.
- NMRC provided RESUS status briefs up the chain of command to Navy legal, BUMED and Navy Surgeon General, as well as to NMSC (RDML Turner).

- NMRC continues communication with recruited/potential study sites, providing study status updates as appropriate.

Challenges:
The RESUS trial seeks to enroll gravely injured patients in the pre-hospital environment. The process of consent is quite different from that in a trial that would enroll stable volunteers utilizing an informed consent process. Victims of significant trauma and hemorrhagic shock are generally unable to provide such consent. Therefore, patient enrollment in RESUS depends on the application of a Waiver of Informed Consent (WIC) as described in CFR 50.24. Because of the special circumstances of a WIC type trial, the FDA process of review is much more critical and systematic than would otherwise be expected. Nonetheless, this ambitious project continued to progress during 2006.

Major project: Advanced Hemostatic Agents

Description:
Hemorrhage (extreme loss of blood) continues to be the leading cause of death on the battlefield, and over 90% of combat deaths take place before reaching the field hospital. Bleeding from an extremity injury (currently the most common anatomical site of battlefield injury) can potentially be controlled in the pre-hospital phase by direct compression and application of a dressing. Advanced hemostatic agents are urgently needed to save warfighters' lives. QuikClot® (Z-Medica Corp., Wallingford, CT), a granular zeolite material, showed promising results in animal trials and was quickly deployed to OEF/OIF. While effective, this product has disadvantages of heat generation at the wound site and difficulty of removal. Establishment of appropriate animal models of complex injury enabled further studies on modified QuikClot® and other hemostatic materials.

Milestones:
- Aug 06. Completed preclinical study demonstrating that QuikClot® Advanced Clotting Sponge was as efficacious as the original QuikClot® granules in inducing hemostasis and improving survival in a porcine model of uncontrolled hemorrhage. These findings provided critical information for MARCORSYSCOM Medical Acquisition to down-select hemostatic agents for deployment in Marine Corps IFAK (individual first aid kit).
- Nov 06. Completed preliminary studies demonstrating relative efficacy of novel (non-exothermic) formulation of QuikClot ACS+ ("Cool Clot").
- Dec 06. Awarded MARCORSYSCOM funding to perform comprehensive study regarding effectiveness of advanced hemostatic agents in combat relevant models of uncontrollable hemorrhage.

Major project: Operation of a multiple large animal chamber (MLAC) hyperbaric facility and study of hyperbaric hyperoxic lung injury.

Description:

Naval Medical Research Center (NMRC) is the DoD center of excellence for hyperbaric research involving animal models. NMRC had the capability to conduct research on one

20 kg swine model but needed the capability to use multiple swine, and larger animals. Many of NMRC's undersea medicine research protocols require utilization of 70 kg swine models to better simulate the mass of a human subject (DoD divers and Navy submariners exposed to hyperbaric stress). In 2005, the effort to provide an enhanced research chamber capable of studies involving up to four 20 kg swine models or two 70 kg swine models was completed. The chamber is 7 feet in diameter, 16 feet long and weighs approximately 22,000 lbs. This capability has been a major enabler of research at NMRC to develop treatment procedures for decompression sickness with close relationship to human outcomes based on the weight of the species studied.

In addition to significant work regarding decompression sickness, we have made advancements in the study of hyperbaric hyperoxic lung injury utilizing ex vivo lung slices (precision cut lung slices) in a hyperbaric environment and small animal chambers able to measure respiratory parameters while in a hyperbaric environment.

Milestones:

- Jul 06. Demonstrated a safe decompression from 132 feet of sea water in 14 hours of decompression time.
- Dec 06. Demonstrated that oxygen pre-breathe of 15 minutes prevents decompression sickness in dropout decompression from 60 feet of sea water.
- Nov 06. Initiated a study of standard operating and emergency operating procedures for staged decompression from 132 feet of sea water in a disabled submarine rescue scenario.
- Nov 06. Initiated a study of intravenous perfluorocarbons in the treatment of severe DCS.
- Jun 06. Modified a hyperbaric chamber for the study of lung slices in a hyperbaric environment.
- Oct 06. Designed and constructed small animal hyperbaric chambers with the capability to measure respiratory tracings in a hyperbaric environment.

Infectious Diseases Directorate (04)

Viral and Rickettsial Diseases Department (VRDD)

The principal goals for the Viral and Rickettsial Diseases Department (VRDD) are to develop protective vaccines against dengue and scrub typhus, and to devise rapid point-of-care assays to aid military medical personnel in diagnosing these diseases under operational conditions. During 2006, significant progress was made in achieving these goals with accomplishments ranging from important basic science research discoveries to the initiation of a Phase I human trial of a prototype dengue virus DNA vaccine.

Viral Diseases Research

Dengue vaccine development
Efforts began in the mid 1990's to develop a dengue vaccine using the nucleic acid immunization approach. The prototype was a dengue-1 DNA vaccine that underwent extensive small and large animal testing. This vaccine was shown to produce moderate

to high levels of anti-dengue virus neutralizing antibodies that provided 85% to 90% protection against live virus challenge in a non-human primate model.

In FY06, we began the first-ever human trial using the prototype vaccine. The study is an open-label, dose escalation, Phase I safety, and immunogenicity trial of a dengue serotype 1 premembrane (prM) and envelope (E) DNA vaccine (D1ME100) in healthy adults. Twenty-four adult volunteers are to receive D1ME100 in three doses to document the safety and neutralizing (NT) antibody / cell mediated immune responses, as an early test of concept for the dengue DNA vaccine. Subjects are divided into two groups of 12 subjects each (minimum of 10) with one group receiving1 mg of vaccine (low dose group) and the other receiving 5 mg of vaccine (high dose group). At the time of this report, the low dose group immunizations have been completed. The vaccine has been well tolerated and the immunogenicity results are pending. Twelve subjects in the high dose group have been given two doses, with the third dose scheduled for March of 2007.

Investigators in the department are also working on two other novel approaches to dengue vaccine development that utilize two non-replicating viral vectors, adenovirus and Venezuelan Equine Encephalitis (VEE) replicons. The adenovirus work is being conducted in collaboration with GenPhar, Inc. To date a tetravalent formulation has been manufactured consisting of two constructs, one that expresses the prM and E proteins of dengue-1 and dengue-2, and the other that expresses the prM and E of dengue-3 and dengue-4. The tetravalent vaccine formulation is generated by combining the two constructs. When the tetravalent formulation was administered in two intramuscular injections eight weeks apart, high levels of tetravalent anti-dengue neutralizing antibody were generated in non-human primates. Live virus challenge studies conducted one month after the last dose demonstrated a high level of protection against all four dengue serotypes. Challenge results six months after the last dose are pending. Plans are being formulated to evaluate the safety and immunogenicity of the dengue tetravalent adenovirus vaccine candidate in a Phase I human study.

Proof-of-concept studies using a VEE replicon vaccine against dengue-I have been completed in non-human primates. The replicon vaccine was engineered to express the prM and E proteins of dengue-1 West Pac 74 strain. Groups of four monkeys were immunized with the dengue-1 VEE replicon (VRP), the dengue 1 DNA vaccine, or a combination of the two in a DNA prime-VRP boost regimen. Anti-dengue neutralizing antibody responses were similar in animals immunized with either the DNA alone or the VRP alone. The highest neutralizing antibody titers were generated when the VRP was administered with the DNA vaccine in a DNA prime-VRP boost regimen. Anti-dengue T cell responses however were only evident in animals immunized with either the DNA

alone or the prime-boost regimen. All together, these data support advancing to a Phase I human trial of the prime-boost vaccine regimen to evaluate proof-of-principle.

In collaboration with Vical Inc., a proprietary lipid-based adjuvant was evaluated for its ability to enhance the immunogenicity and protective efficacy of a tetravalent DNA vaccine. Compared to the tetravalent DNA vaccine alone, anti-dengue neutralizing antibodies were two to twenty-fold higher when the tetravalent DNA vaccine was formulated in the Vical adjuvant. When animals were challenged with live dengue-2 virus, significant protection was demonstrated with two of four immunized animals

showing no viremia and one animal each showing one and two days of viremia. Funding is currently being sought to repeat the non-human primate study with a tetravalent challenge and to conduct a Phase human trial of safety and immunogenicity.

Dengue Immunology

It is widely known that infection with a given dengue virus serotype results in life-long protective immunity. To develop the most efficacious vaccine possible, one must understand the factors involved in generating protective immunity following naturally acquired infection. Studies are being conducted by VRDD investigators to fully identify factors related to protective immunity against dengue and to further define the pathogenesis of severe dengue disease. The interactions between antigen-presenting dendritic cells and dengue virus are being examined to determine how these antigen presenting cells process foreign dengue virus proteins to generate protective antibody and cellular immune responses.

Field studies of natural dengue infection conducted in the OCONUS infectious diseases labs have shown that many individuals infected with dengue manifest changes in their immune system to include leukopenia, thrombocytopenia and alterations in T cell and dendritic cell function. Scientists in VRDD are conducting in vitro experiments to understand how dengue effects these changes.

As stated earlier, the presence of anti-dengue neutralizing antibody has been shown to correlate with protection against dengue infection. Current methods to measure dengue neutralizing antibody are cumbersome and very time-consuming (requires 5 to 10 days to complete). VRDD investigators have developed a novel high-throughput assay that is capable of measuring neutralizing antibody in 24 to 48 hours. Work conducted this year compared this new assay with the gold standard plaque-reduction neutralization assay. The results showed that the new high-throughput assay performed comparably to the standard plaque reduction neutralization test. Having a high throughput assay to measure anti-dengue neutralizing antibody is critical to the success of large Phase II and III clinical trials that involve hundreds to thousands of study subjects.

Dengue Diagnostics

Since no protective vaccine or specific treatment options are available for dengue fever, accurate diagnosis is critical to curtail epidemic spread and reduce manpower losses due to this disease. Currently, there are no diagnostic kits, which are cleared by the Food and Drug Administration (FDA), available for rapid detection of dengue infection within the United States. Apart from benefits to the US civilian population, the availability

of such diagnostics would be especially valuable for the military. During missions in endemic regions, a quick and accurate diagnosis can enable a Commanding Officer to make better decisions regarding the medical needs of their military personnel. To address this deficiency, the dengue diagnostics group focused its efforts on identifying the most promising point-of-care (POC) dengue antibody assays developed by commercial partners. The best performing assay will be down-selected for further validation through clinical trials, and submitted in a 510(k) application to the FDA for approval.

The group made significant progress towards down-selecting the most promising rapid diagnostic assay. In FY 06, a number of commercial products were tested including dengue antibody assays developed by Panbio, Inc., Binax, ANP Technologies, Inc., Quantum Design, Inc., VecTOR Test Systems Inc., and InBios. Preliminary data indicate that Panbio is the front runner and has shown a high degree of sensitivity and specificity in our tests so far. While we are continuing our collaborations with the other commercial partners, we have selected Panbio as the most promising candidate for clinical testing.

This year, PanBio, Inc. (Columbia, MD) and Naval Medical Research Center (NMRC) finalized a formal agreement, which allows NMRC to evaluate the newly re-formatted dengue Duo IgG and IgM diagnostic device manufactured by PanBio, Ltd., Queensland, Australia. Evaluation of an earlier device by Panbio Ltd., the Dengue Rapid Immunochromatographic Card Assay, using whole virus antigen for detection of IgG and IgM found that the device had high sensitivity and specificity. A new re-formatted Duo IgG and IgM device using safer dengue recombinant antigens also has the ability to differentiate between primary and secondary infections, can use either whole blood or serum, and has shown 94.5% sensitivity and 85.7% specificity in a clinical trial conducted in Sri Lanka. At NMRC, preliminary evaluation showed 100% sensitivity and specificity using a limited number of primary infection, secondary infection, and negative control samples and comparing them to a microplate ELISA standard. Efforts are currently underway to conduct field testing of the PanBio assay using sera collected in DoD-approved prospective studies in collaboration with OCONUS laboratories overseas. The results of these studies will be compiled to prepare a Pre-market Notification 510(k) to the FDA for clearance, projected to be completed by FY 09.

Another thrust area of the dengue diagnostics group is the development of a dengue antigen assay. There is currently no rapid diagnostic kit available for the direct detection of dengue viral antigens. Most commercial products that have been evaluated detect immune responses to dengue infection, by assaying for anti-dengue antibodies. This is partly due to the great sensitivity required to detect virus in serum or whole blood. During the initial stages of dengue infection however, there is inadequate expression of host immune response elements for serological detection methods to work effectively. An antigen-based assay would therefore allow earlier detection and diagnosis of the causative agent behind an observed fever. While work has begun on the development of the dengue antigen assay, it has been deemed a lower priority than the evaluation and optimization of serum IgG/IgM assays developed in collaboration with commercial partners.

In addition to antigen and antibody detection assays, the diagnostics group has been working closely with Tetracore, Inc. to produce a dengue real-time RT-PCR assay that is both group and serotype specific for dengue. Such an assay would be used for hospital diagnosis and would reduce the amount of time needed for a confirmatory diagnosis from several days to several hours. Tetracore dry format real-time RT-PCR assays for detection and serotyping of dengue viruses have been evaluated using monkey viremic samples. We concluded that the Tetracore real-time RT-PCR assays are sensitive and specific enough to move forward to testing human clinical samples. When tested with human clinical samples, the dengue group assay exhibited 98.9% sensitivity and 100.00% specificity with an extensive cross-reactivity panel and normal human sera

samples. This dry-format, real-time RT-PCR assay can detect all four dengue serotypes to low titers of viremia, and does so in two hours, a fraction of the time required for comparable diagnostic assays. The group assay requires minimal technical expertise, is stable at ambient temperatures, and is field deployable for the detection of dengue virus.

Current progress of dengue diagnostics program has paved the way towards the availability of two rapid hand-held assays to diagnose dengue infections-- one assay for the detection of IgM antibodies specific to dengue virus and the other assay for the detection of dengue virus in serum or whole blood.

Rickettsial Diseases Research

Vaccine Research

We have identified two vaccine candidates: the recombinant antigen of 56 kDa antigen (r56) and the DNA plasmid of 47 kDa (HtrA). Both have been shown to provide very good homologous protection. The conserved 47 kDa provides better cross protection in few strains. However, blast search has found that the 47 kDa antigen exhibits sequence homology with human serine protease. By genetic manipulation of the 47kDa gene, a plasmid construct without the homologous region has been made. We are in the process of confirming the expression of the truncated protein antigen. One of these candidates will be selected for pre-clinical trials in FY08. A new r56 from strain TA763 has been cloned, expressed, purified, and refolded. The final product has the potential to be included in a cocktail for broad protection.

Diagnostic Assays

RDD collaborated with AccessBio in the SBIR Phase II production of a handheld, soldier friendly, field assay for diagnosing scrub typhus utilizing our three Orientia tsutsugamushi recombinant proteins Kp r56, Kt r56 and Gm r56. Use of our state-of-the-art rickettsial quantitative real-time PCR assays and multilocus sequence typing: 1) we have detected Rickettsia parkeri in skin biopsies of eschar and rash in a military patient bitten by an infected tick from Tidewater region of Virginia. This was only the third reported case of R. parkeri rickettsiosis and the second in a military person; 2) detected R. felis in a febrile patient from Egypt (first reported case of R. felis rickettsiosis in Egypt); detected R. montanensis, R. amblyommii and R. felis in ticks removed from DoD personnel and their dependents. This has heightened the awareness of the risk to military personnel of infection with rickettsial agents; detected for the first time R. felis in Xenopsylla cheopis (oriental rat flea) the arthropod vector for plague and murine typhus.

VRDD investigators are continuing efforts to validate the Rickettsia-specific and the O. tsutsugamushi-specific assays with the goal of obtaining sufficient data to request FDA 510k approval of a diagnostic kit to include these two assays.

Investigators have also characterized and evaluated the host gene response to rickettsial infections of human peripheral blood cells and the monocytic cell line-THP-1. This was done as a means to quickly and specifically diagnose rickettsial diseases and Q fever.

Many recombinant antigens of R. typhi (murine typhus, fragment AN), Coxiella burnetii (Q fever, Com-1), Bartonella bacilliformis (Oroya fever, Pap31) have been prepared for disease specific antibody detection. The recombinant protein fragments of the OmpB

antigen from typhus group rickettsiae were purified and ready for methylation. The full ORF for OmpB and OmpA of SFG rickettsiae (R. conorii and R. rickettsii) have been cloned.

The recombinant Pap31 has been further purified, and evaluated in an ELISA format from more than 300 patient sera. The sensitivity and specificity strongly suggests that this recombinant antigen can be used to develop a rapid flow assay.

Risk Assessment/Epidemiology

We assessed the risk of tick-borne rickettsial diseases for military personnel. The presence of rickettsial DNA in epidemiologic samples was determined for arthropod, rodent and human samples. In a patient in Thailand the genus-specific and the tick-borne SFG rickettsia-specific qPCR assays detected the DNA of Rickettsia honei, a pathogen of Thai tick typhus. We have developed and optimized an R. montanensis and an R. amblyommii-specific qPCR assays to determine whether these agents are found among ticks (Dermacentor variabilis, Ixodes scapularis and Amblyomma americanum) collected from patients at military health care centers. The assays successfully detected R. montanensis and R. amblyommii in the ticks assessed.

We determined that the prevalence of antibodies specific for human granulocytotropic anaplasmosis (HGA) agent Anaplasma phagocytophilum and spotted fever group rickettsiae (SFGR) for 10,000 military personnel was 0.1% and 6.0%, respectively. Initial studies began in 2006 to evaluate the risk of rickettsial diseases among military personnel deployed to South Korea by evaluating sera from 10,000 military personnel previously stationed in South Korea. These results show that military personnel are no more likely to be infected with A. phagocytophilum or SFGR than non-military personnel living in the United States

Reagent Repository Program

NMRC has one of the largest collections of various rickettsial pathogens in the world. We provide qPCR primers, probes, and standards for qPCR assays and reagents, both recombinant proteins (e.g. Kp r56) and whole cell antigens derived from cultures, for serological assays and molecular detection to overseas laboratories (NAMRU-3, AFRIMS, NAMRU-2, NMRCD), SBIR contractors and the Department of Homeland Security.

Genomics

In collaboration with TIGR, two scaffolds of Orientia tsutsugamushi (Karp strain) genome have been assembled. One is 2.0 Mb and the other is 0.89 Mb. The genome sequence is more than 90% completed and has revealed many unique features of Orientia unkown to scientists in the field.

Proteomics
The combination of 2D gel electrophoresis and LC-MS/MS has confirmed the presence of post-translational modification of major outer membrane proteins of SFG Rickettsiae. The knowledge obtained will facilitate the development of good diagnostic reagents.

Enteric Diseases Department (EDD)

Overview

The Enteric Diseases Department continued a period of heightened activity during 2006, executing or wrapping up four Phase I/II clinical trials while advancing several new generation vaccine candidates against enterotoxigenic E. coli (ETEC) and Campylobacter jejuni further into animal evaluation. Its strong foundation of basic research catalyzed the generation of new vaccine concepts, some of which have resulted in U.S. patent applications. In terms of applied research, investigators in the Clinical Trials Branch deftly managed the completion of first-in-human Phase I trials of a subunit vaccine against C. jejuni and a subcellular vaccine against Shigella flexneri 2a. Additionally, research in which Departmental scientists have partnered with academic and industry groups has led to the development of a new human challenge model for ETEC, and laid the groundwork for initiation of clinical trials in 2007 to develop a new C. jejuni volunteer challenge model, which all but eliminates the risk of the post-infectious neurologic sequelae known as Guillain-Barré syndrome.

Several basic research highlights are worthy of mention. Dr. Patricia Guerry's group has identified and characterized a set of novel virulence proteins that are secreted through Campylobacter flagella. The high level of protective immunity elicited by one of these proteins has kindled interest in its potential as a subunit vaccine. Her group has also characterized the role of flagellin glycosylation in microcolony formation on eukaryotic cells. The structural basis of ETEC adhesion to intestinal cells has been further elucidated through a fruitful collaboration between Departmental scientists and the group of Di Xia (Laboratory of Cell Biology, National Cancer Institute).

Leading international experts in bacterial enteric diseases, Departmental researchers have drawn the attention of industry and academic groups with similar interests. A significant new industry partnership was begun in Sep 2006 with ACE Biosciences, Inc. (Odense, Denmark), with the signing of a Cooperative Research and Development Agreement to co-develop a new C. jejuni human challenge model (see above). Such a model is expected to pave the way for the development of new Campylobacter vaccines being developed both by ACE and NMRC. A strong academic partnership was forged between the University of Colorado Health Sciences Center (Dr. Randall K. Holmes' group) and Departmental scientists led by CAPT Stephen Savarino. CAPT Savarino and Dr. Holmes were awarded a 5-year multi-million dollar cooperative research agreement

by the NIAID under the Institute's program of Cooperative Research Partnerships for Biodefense to develop a novel oral delivery system for ETEC adhesin vaccine antigens.

Specific Research Highlights

Campylobacter Vaccine Research and Development

-Comprehensive characterization of two C. jejuni field isolates completed (C. jejuni strains CG-8421 and BH-0100142), including full genome sequencing and annotation and determination of the lipooligosaccharide (LOS) structure of each. These studies demonstrated that each of these candidates for development of a human C. jejuni challenge model lacked enzymatic machinery or structural evidence of sialic acid decoration of surface structures, all but ruling out the possibility of the post-infectious

Guillain-Barré syndrome. Late in 2006, under the ACE Biosciences CRDA, cGMP cell banks of each of these strains was produced at Charles River Laboratories in preparation for human challenge trials scheduled for initiation in Mar 2007.

-Through ACE Biosciences as sponsoring authority, EDD Clinical Trials Branch personnel worked closely with its partners to prepare, submit and get authorization from the U.S. FDA on a new Investigational New Drug/Biologics (IND) application for the use of two C. jejuni strains in human challenge studies. The clinical protocol for the associated strain and dose finding clinical study was submitted to ethical review authorities and at year's end, had been given provisional approval by the NMRC IRB.

-Developed recombinant expression systems and purification protocols to produce research grade lots of five different C. jejuni surface-exposed or secreted proteins. These lots were then used in mouse vaccination-live C. jejuni challenge experiments to inform the down-selection of subunit vaccine candidates for further development.

-Further elucidation of C. jejuni proteins that are secreted through the flagellar apparatus and play a role in virulence. One of these proteins, FspA, has been singled out as a strong subunit vaccine candidate based on its elicitation of a high level of protective immunity against wildtype C. jejuni challenge in the mouse model.

-The Immunology Branch completed all systemic and mucosal immunological testing of clinical samples taken from subjects who had participated in the Phase I clinical trial of a recombinant flagellin vaccine candidate (MBP-Fla). The composite findings that emerged from this work indicate that the MBP-Fla vaccine induced both mucosal and systemic immunity but to a lesser degree than had been anticipated.

-Mouse vaccination-challenge studies were completed to show for the first time that a C. jejuni capsule-conjugate vaccine was efficacious in protecting mice from disease upon subsequence challenge with wildtype C. jejuni. These data served as part of the foundation for a nonprovisional patent application for a capsule-conjugate vaccine against C. jejuni.

Enterotoxigenic Escherichia coli Vaccine Research and Development

-In the first half of 2006, investigators in the Clinical Trials Branch partnered with Drs. AL Bourgeois and R McKenzie at the JHBSPH, where a Phase IIb inpatient clinical trial was completed to evaluate the passive oral protective efficacy of hyperimmune bovine milk anti-adhesin IgG preparations against homologous ETEC challenge. The results of this trial provided clear proof of principle that anti-ETEC adhesin antibodies can confer protection against ETEC diarrhea.

-In the latter half of 2006, the JHBSPH/NMRC clinical research teams partnered to conduct and complete a volunteer challenge trial in which ETEC that express the fimbrial colonization factor CS17 was given to volunteers at two dose levels. A strain and dose was derived from this trial that is expected to consistently result in ≥ 80% diarrhea attack rate. This study provided corroborative evidence for the importance of CS17-ETEC as a cause of human disease, and laid the groundwork for a subsequent oral passive

vaccination-CS17-ETEC challenge study scheduled for initiation in the first months of 2007.

-A research team in the Molecular Biology and Biochemistry Branch designed and developed a recombinant system for expression of stable, donor-strand-complemented CotD protein (i.e., dscCotD), the minor adhesive subunit of CS2 fimbriae of ETEC. An initial research grade lot of this antigen was produced and used to initiate mouse comparative, mucosal immunogenicity studies of this the third tier adhesin slated for incorporation into a trivalent adhesin-based ETEC vaccine.

-Donor strand complementation technology was also used to engineer and produce research grade lots of dscCstH, the recombinant adhesin derived from the ETEC colonization factor CS3. Mouse mucosal immunogenicity studies conducted with this antigen vs. CS3 indicated less than desired immunogenicity of dscCstH, driving expanded research to develop alternate recombinant forms of this adhesive antigen.

-Based on the compilation of work completed within the EDD over the past four years, a shift in ETEC vaccine research has occurred with focus now solidly on the development of an adhesin-based ETEC vaccine. An important hurdle to overcome along this R&D pathway is the development of a suitable mucosal delivery system for these adhesins that simultaneously incorporates a toxoid component. The first line approach for overcoming this hurdle involves the engineering of adhesin-enterotoxoid chimera molecules, which have the potential for delivering both the ETEC adhesin(s) and non-toxigenic B-subunit of the ETEC heat-labile enterotoxin (LTB) by mucosal immunization. During 2006, work was completed to further develop this approach under a newly awarded NIAID cooperative research agreement. A second adhesin-enterotoxoid chimera, composed of dscCfaE fused to cholera toxin A2 peptide, and noncovalently bound to the B-pentamer of LT, was engineered by partners at the University of Colorado. In Dec 2006 a small research grade lot of this chimera (dscCfaE-CTA2/LTB5) was produced, as was a second larger lot of the original adhesin-enterotoxoid chimera (dscCfaE-CTA2/CTB5). These materials were undergoing extensive biophysical and biochemical characterization at the time of writing and had been incorporated into animal vaccination experiments planned for the first half of 2007.

-Comparative mucosal immunogenicity studies were completed in mice with the second-tier ETEC adhesin dscCsbD showing that it elicits functional antibody responses that are significantly greater than those induced by comparable doses of whole CS17 fimbriae.

-A comprehensive mutational analysis was performed of the lead ETEC adhesin dscCfaE, the results of which allowed us to define the location and contour of the receptor-binding domain of CfaE, and to define the relative importance of intramolecular disulfide bonds in the maintenance of the structural and functional integrity of native CfaE.

-Investigators at NMRC worked in close collaboration with CDR Eric Hall and others at NMRCD as they performed the initial Aotus nancymae mucosal immunization studies with the lead ETEC adhesin vaccine component, dscCfaE. Studies in which dscCfaE

was given to monkeys by the intranasal route demonstrated the inherent immunogenicity of this antigen in nonhuman primates for the first time.

Shigella Vaccine Research and Development

-The Immunology Branch completed all mucosal immunological testing of clinical samples taken from subjects who had participated in the Phase I clinical trial evaluating a subcellular S. flexneri 2a vaccine (so-called Invasion-complex or Invaplex vaccine). Based on the composite findings that emerged from this work, the Invaplex vaccine was scheduled for testing in additional Phase I and IIb clinical trials in 2007.

New or Ongoing Collaborations/Cooperative Research and Development Agreements

-Dr. Patricia Guerry established a new collaboration with Dr. Edward H. Egelman, Professor, Department of Biochemistry and Molecular Genetics, University of Virginia Medical School. She is providing Dr. Egelman's laboratory purified genetically modified C. jejuni flagella for the determination of its 3 dimensional structure at high resolution.

-Dr. Guerry established a new collaboration with Dr. Hye-Jeong Yeo, Assistant Professor, Department of Biology and Biochemistry, University of Houston. Dr. Yeo is a X-ray crystallographer who has begun working on the structural determination of selected C. jejuni virulence proteins.

-Dr. Guerry continued to closely collaborate with Dr. Mario Monteiro, Professor of Chemistry, University of Guelph, who is the co-inventor of capsule-conjugate vaccine approach to C. jejuni and the chemist who has developed the specific protocols being used to derive capsule and conjugate it to CRM197.

-In an ongoing collaboration between CAPT Savarino and Dr. Di Xia (Head, Crystallography Unit, Laboratory of Cell Biology, National Cancer Institute), Dr. Xia's group solved the crystal structure of the major subunit of CFA/I fimbriae (CfaB). This is one of the very first major fimbrial subunits for which the crystal structure has been solved. The completion and publication of this work is expected during 2007. Dr. Xia's

group has also defined conditions for the crystallization of two other structures, one of which is an auxiliary protein involved in CFA/I fimbrial biogenesis and the other a subunit of CS3 fibrillae. X-ray diffraction and phasing data are being collected on these proteins.

-CRDA established with ACE Biosciences for the co-development of a new, safer C. jejuni volunteer challenge model (see elsewhere in this report for more details).

-The multiparty CRDA between NMRC, the JHBSPH, ImmuCell Corporation, and the WRAIR continued during 2006, under the umbrella of the Peer-Reviewed Medical Research Program Grant entitled 'Development of a bovine milk immunoglobulin supplement that prevents travelers' diarrhea by blocking pathogen adherence.' See elsewhere in the report for details of 2006 research findings under this grant/CRDA.

-A Clinical Trials Agreement (CTA) between NMRC and USAMMDA was written and distributed for review and signature in Dec 2006. The purpose of this CTA was to allow

the continuance of joint NMRC/WRAIR clinical research that is designed to further the testing and evaluation of S. flexneri 2a Invaplex vaccine.

Invited Speakers/Departmental Guests

On 1 Feb 2006, the Enteric Diseases Department (EDD) hosted the visit of Dr. A. Louis Bourgeois, Associate Professor of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore MD. As part of his visit, Dr. Bourgeois gave a seminar entitled 'Protective Efficacy of an Inactivated Whole Cell ETEC Vaccine in Travelers to Guatemala and Mexico: Impact of Disease Severity and Vaccine "Take" on Outcome.' Sponsored by the NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

On 15 Feb 2006, EDD hosted the visit of Dr. Cheryl Spence, a post-doctoral fellowship candidate from the Department of Microbiology and Immunology, The Brody School of Medicine, East Carolina University. As part of her visit, Dr. Spence gave a seminar entitled 'Characterization and Regulation of an Oxygen Induced Starch Utilization Operon in the Obligate Anaerobe Bacteroides fragilis.'

On 22 Feb 2006, EDD hosted the visit of Dr. Srinivas Narasipura, a post-doctoral fellowship candidate from the Division of Infectious Diseases Wadsworth Center, New York State Department of Health, Albany, NY. As part of his visit, Dr. Narasipura gave a seminar entitled 'Characterization Superoxide dismutases play crucial roles in the pathobiology of the human fungal pathogen Cryptococcus gattii.'

On 15 Mar 2006, EDD jointly hosted the visit of Dr. Arvind Bhagwat, U.S. Department of Agriculture. As part of his visit, Dr. Bhagwat gave a seminar entitled 'My Gut Feelings on Ever Mutating Foodborne Pathogens: How Escherichia coli Manages Best of Both Worlds in and out side the Host.' Sponsored by NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

On 29 Mar 2006, EDD hosted a seminar given by Dr. Chien-Chung Chao, Viral and Rickettsial Diseases Department, IDD, NMRC. The seminar was entitled 'Qualitative and Semi-Quantitative Analyses of Rickettsia prowazekii Proteomes: A Comparative Proteomic Study using 2D-LC/MS/MS and 2D-PAGE.' Sponsored by NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

On 19 Apr 2006, EDD hosted the visit of Dr. Julianne Rollenhagen, a post-doctoral fellowship candidate from the Infectious Diseases Division, Massachusetts General Hospital, Boston MA. As part of her visit, Dr. Rollenhagen gave a seminar entitled 'Immunogenicity of Transcutaneously Applied V. cholerae Antigens.'

On 14 Jun 2006, EDD hosted the visit of Dr. Dennis Kopecko, Director of the Enteric and Sexually Transmitted Diseases Section, Center for Biological Evaluation and Research (CBER), Food and Drug Administration. As part of his visit, Dr. Kopecko gave a seminar entitled 'Development and Animal Testing of Live, Attenuated Oral Vaccine for protection

against Anthrax.' Sponsored by NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

On 20 Jun 2006, EDD hosted the visit of Dr. James Versalovic, Baylor College of Medicine. As part of his visit, Dr. Versalovic gave a seminar entitled 'Probiotic Lactobacilli for Intestinal Fortitude.' Sponsored by NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

On 12 Jul 2006, EDD hosted the visit of Dr. Amit Balakrishnan, a post-doctoral fellowship candidate from the Department of Physiology & Biophysics, University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School, Piscataway, NJ. As part of his visit, Dr. Balakrishnan gave a seminar entitled 'A Novel Candidate Anti-Chlamydial Target Identified With Metalloprotease Inihibitors.'

On 19 Jul 2006, EDD hosted the visit of Dr. Eileen Barry, Associate Professor of Microbiology and Immunology, Center for Vaccine Development, University of Maryland School of Medicine. As part of her visit, Dr. Barry gave a seminar entitled 'Live Attenuated Francisella tularensis Vaccine Strain Development.' Sponsored by NMRC/WRAIR Combined Diarrheal Diseases Prevention Research Program.

Key Appointments/Milestones

1. Dr. Patricia Guerry was nominated and elected as the Campylobacter Vaccine Working Group Leader for the Military Infectious Diseases Research Program, USAMRMC, in January 2006 upon the transition of LCDR Thomas E. Hickey out of this role. Over the course of 2006, Dr. Guerry provided robust leadership in this position, overseeing increasing CONUS-OCONUS research interactions and the development and signing of a Cooperative Research and Development Agreement with ACE Biosciences, Inc. (Odense, Denmark).

2. Dr. David Tribble was awarded the Navy Meritorious Civilian Service Award, the Navy's third highest civilian award, in Aug 2006. Dr. Tribble was recognized as one of the Navy's premier clinical scientists working to develop new enteric vaccines to meet significant military needs in this arena, as well as a leading DoD expert on the ethical conduct of clinical trials.

3. With the departure of Dr. David R. Tribble in July 2006, CAPT Joyce Lapa was appointed as the Acting Head, Clinical Trials Branch, Enteric Diseases Department.

4. Dr. David Tribble was appointed as a Guest Researcher, Enteric Diseases Department, NMRC in July 2006, upon taking an academic position as tenure-track Associate Professor of Biometrics and Preventive Medicine, and Associate Director of the Infectious Diseases Clinical Research Program USUHS in July 2006. Over the second half of 2006, Dr. Tribble continued to provide vital leadership in the planning and execution of clinical research within the Department and Diarrheal Diseases Prevention Research Program as a whole.

5. CAPT Joyce Lapa was appointed as a voting member of the NMRC Institutional Review Board in July 2006.

6. In July 2006, HM1 Junio Colobong was selected as the Command's Sailor of the Half-Year. HM1 Colobong was the first petty officer in the Enteric Diseases Department who was so recognized in more than a decade. His citation emphasized his substantial contributions as a biochemistry laboratory technician, and as the Departmental safety officer.

7. Dr. Shahida Baqar received academic appointments as Adjunct Assistant Professor of Preventive Medicine and Biometrics and Adjunct Assistant Professor of Pathology at the USUHS in 2006.

8. CAPT Stephen Savarino was awarded a five-year, four million dollar cooperative research agreement by the National Institute of Allergy and Infectious Diseases (NIAID) entitled 'Development of an Adhesin-Toxoid Chimera Vaccine for Enterotoxigenic E. coli.' The proposal was prepared by CAPT Savarino (PI) in collaboration with Dr. Randall K. Holmes (Associate PI) at the University of Colorado Health Sciences Center. Funding for this agreement, which is being managed through the Office of Sponsored Programs, Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF), was begun on 1 Aug 2006, and is slated to continue, pending annual non-competing renewals, through 31 Jul 2011.

9. LT Colleen Carpenter was awarded a new Navy In-House Laboratory Independent Research (ILIR) grant in Oct 2006. Her ILIR proposal, entitled 'Infant Mouse Susceptibility to Human-Derived Enterotoxigenic Escherichia coli,' was ranked second among 70 proposals that were submitted from throughout the Navy Medical R&D enterprise.

10. LT Stephanie Sincock was one of a small number of nominees for the NMRC Junior Officer of the Year for 2006. Her nomination was cited in a Letter of Commendation from the Commanding Officer in which she was lauded for her exemplary scientific work and contributions to the preclinical development of a new ETEC vaccine and for her contributions to Command morale and welfare as Wardroom President.

11. LCDR Mark Riddle officially reported for duty at the Command in Dec 2006. LCDR Riddle had previously been stationed at NAMRU-3, Cairo, Egypt. LCDR Riddle joined the Clinical Trials Branch and immediately began to make contributions as the research liaison with OCONUS laboratories.

Visitors

From 1 Jan to 28 Feb 2006, Dr. Hanan El Mohamady spent an extended Temporary Duty at NMRC. A Foreign Service National scientist stationed at the U.S. NAMRU-3, Cairo, Dr. El Mohamady was the recipient of a UNESCO-ASM Travel Award from the American Society for Microbiology. She spent 2 months working in the Immunology Branch, Enteric Diseases Department, working closely with LT Colleen Carpenter and under the sponsorship of CAPT Stephen Savarino, completing a research project in

which she evaluated serum antibody levels against a prototype ETEC fimbrial adhesin in Egyptian infants, children and adults.

On 17 Feb 2006, CAPT Stephen Savarino and others in the Enteric Diseases Department, NMRC and Enteric Infections Department, WRAIR, hosted an On-site meeting with representatives from BioVentures for Global Health and Boston Consulting Group and provided overview brief on Joint Army-Navy Enteric Diseases research program and vaccine development efforts. These groups were commissioned by the Bill and Melinda Gates Foundation to develop a landscape analysis of diarrheal diseases vaccines opportunities, requirements and business plan analysis. This meeting was part of a series in which BVGH and BCG met with research and policy leaders in this research area. Visitors included Wendy Taylor, Executive Director, and Christopher Earl, CEO, BioVentures for Global Health.

On 26 May 2006, research leaders in EDD held an On-site meeting with ACE Biosciences, a Danish Biotechnology company with an investigational Campylobacter vaccine, to further develop the goals and statement of work for a CRDA, which was later signed in Sep 2006. Under this CRDA, ACE is sharing costs for co-development of a new and safer Campylobacter jejuni human challenge model for future use in testing the efficacy of ACE and DoD-developed vaccines.

On 15 Jun 2006, CAPT Stephen Savarino hosted the third annual meeting of collaborating Site investigators for the Peer Reviewed Medical Research Program (PRMRP) grant entitled 'Development of a Bovine Milk Immunoglobulin Supplement that Prevents Travelers' Diarrhea by Blocking Pathogen Adherence.' Over twenty scientists and staff from outside NMRC attended this meeting, with contingents from the Johns Hopkins Bloomberg School of Health led by Drs. A. Louis Bourgeois and Robin McKenzie, and that from NMRCD Lima led by CDR Eric Hall.

On 2 Aug 2006, Dr. Robert Bargatze (CSO, LigoCyte Pharmaceuticals, Inc.) visited NMRC to discuss his company's progress in the development of a norovirus vaccine. He met with CAPT Stephen Savarino, who serves as the Military Infectious Diseases Research Program (MIDRP) ad hoc Task Leader for Norovirus Vaccine Research. LigoCyte receives Congressional Special Interest funding for norovirus research and this is administered through MIDRP, USAMRMC.

On 4 Aug 2006, CAPT Stephen Savarino convened an On-site meeting with representatives from Sanofi-Pasteur Vaccines. Visitors included Dr. Daniel Gordon, VP Clinical Affairs; and Dr. Robert Ryall, Director. This meeting, requested by Sanofi-Pasteur, explored potential areas of common interest between DoD and Sanofi-Pasteur in the area of bacterial vaccine R&D, and involved leaders from WRAIR and NMRC in Diarrheal Diseases Prevention Research and Meningococcal Vaccine development.

On 30 Aug 2006, Drs. Patricia Guerry and David Tribble convened a rehearsal meeting for an upcoming FDA Pre-IND Meeting. Visitors included the CSO and CEO from ACE Biosciences, Inc. The IND under development was for two wildtype Campylobacter jejuni strains derived from DoD studies (AFRIMS, Bangkok, Thailand) and commercially processed/manufactured into cGMP cell banks for human use. Through a CRDA with

ACE Biosciences, EDD NMRC is co-developing new, safe human challenge model for C. jejuni that is designed for future use in vaccination-challenge studies to evaluate DoD C. jejuni vaccine candidates as well as those of the corporate partner. In late 2006, the IND package for the C. jejuni challenge strains was successfully submitted.

On 12 Sep 2006, CAPT Stephen Savarino convened an On-Site meeting with representatives from AVANT Therapeutics, Inc., Cambridge, MA to explore potential areas of common interest between DoD and AVANT in the area of enteric vaccine R&D. Visitors included Timothy Cook (AVANT Chief Operating Officer), and Kevin Killeen (AVANT Chief Scientist).

From 1 Oct to 24 Dec 2006, Dr. Barbara Martinez was a visiting Allergy/Immunology/Rheumatology fellow doing research within the Enteric Diseases Department. Dr. Martinez, a fellow at the Baylor College of Medicine, Houston, TX, initiated a research project to determine the prevalence and distribution of colonization factor fimbriae of enterotoxigenic Escherichia coli (ETEC) among ETEC isolates derived from U.S. students studying in Guadelajara, Mexico between 1998-2005. Dr. Martinez' plans are to continue the project (started under the direction of CAPT Savarino) back in Houston in the laboratory of Dr. Bert DuPont at University of Texas.

On 6 Dec 2006, CAPT Savarino hosted an On-Site Meeting with LigoCyte Pharmaceuticals, Inc. to receive a progress update from LigoCyte on their norovirus vaccine development program. Attendees at this meeting included Dr. Robert Bargatze, CSO, LigoCyte; COL David Vaughn, Director, MIDRP, and CAPT Mark Beavers, Navy Liaison, MIDRP.

Malaria Department

Malaria Program 2006

Parasitology

1. Establishment and maintenance of the life cycle of murine, non-human-primate, and human malaria parasites; and participation in the conduct of human volunteer malaria challenge studies. Funded by MIDRP.

2. Conducted Parasitology Tutorial Sections with 2nd year medical Students at the University of Maryland at Baltimore (UMAB) School of medicine

Immunology

1. Continued collaborations with the National Institute of Allergy and Infectious Disease (NIAID) and Noguchi Memorial Institute for Medical Research in Ghana through agreement/grant funded by (NIAID). Trained 6 research associates on the conduct of Immunological Assays in Support of Malaria Vaccine Trials.

2. Conducted experiments aimed at discovering new antigens predicted by the genome project as possible new targets for T-cell immunity in both *P. yoelii* and *P. falciparum* in collaboration with GenVec, funded by an SRIR.

.... a. *P. yoelii* model: Spleen cells from mice immunized with irradiated sporozoites have been used to screen target cells that have been transfected with plasmids encoding "new" antigens.

.... (1) Sera cells from mice immunized with irradiated sporozoites, un-irradiated sporozoites, un-irradiated sporozoites with drug treatment to control erythrocytic stages, mature liver stage parasites and erythrocytic stage parasites reagents; have been prepared and used to screen *Py* antigens expressed by the Wheat Germ Expression system by investigators in Japan.

.... (2) Preliminary data shows that these stage specific sera have identified "new" *Py* antigens for further evaluation and characterization.

.... b. *P. falciparum* model: In collaborating with spleen cells from mice immunized with plasmids encoding "new" antigens have been tested for their ability to induce antigen specific IFNg responses in the Elispot assay. Possible "new" antigens in both the *Py* and *Pf* have now been identified.

3. Adenevector Expression system:

.... a. Demonstrated the feasibility of using adenovectors expressing *Plasmodium yoelii* antigens to prepare antigen presenting cells that can be utilized to recall *P. yoelii* specific T cell responses from immune animals.

.... b. Identified One “new” antigen (*Py*325), by this screening method that is going to be used in a DNA prime-Adenovector boost to look for protection against challenge with sporozoites

4. Collaborated with Viral Diseases Program to develop an Elispot Assay for the detection of antigen specific T cell responses after immunization with Dengue vaccines.

5. Mentored Research Associates from Sanaria, a CDADA partner, and Science and Engineering Apprenticeship Program (SEAP) students.

Non-Human Primate Vaccine Studies

1. Established a new cultured ELISPOT assay for cryopreserved monkey PBMC;

2. Applied the wheat-germ cell-free expression system (WCES) - produced recombinant *Plasmodium knowlesi* protein into T cell assay. Demonstrated for first time in the world that WCES-generated proteins are toxicity-free and antigenic for both ELISPOT assay and cultured ELISPOT assay. Collaboration with Ehime University through a CRADA.

3. Conducted a 3-dimension T cell assay system to measure effector and memory T cells responses in monkeys that were immunized by a combined vaccine of 4 immunogens (*Pk* CSP, *Pk*AMA1, *Pk* SSP2, and *Pk* MSP1) from *Plasmodium* knowlesi, in the Chinese *Rhesus* Monkey (CRM) vaccine project;

4. Conducted a comparative experiment to measure the histological changes in livers, at day 4 after challenge, between PBS and irradiated sporozoites-immunized monkeys;

5. Conducted a mouse study to evaluate the effects of CEL-1000 administration on T cell responses from the liver and spleen prior to and post *P. yoelii* sporozoites challenge, by flow cytometry-intracellular cytokine staining;

Mechanisms of Immunological Protection:

1. Continued collaboration through an Memorandum of Understanding (MOU) with the National Cancer Institute (NCI) Microarray Facility to use DNA microarrays to profile host gene responses to *P. falciparum* in order to identify immunological correlates of protective immunity in human volunteers and mice immunized with irradiated sporozoites. Funded by MIDRP.

2. Finalized studies to develop an assay for a surrogate marker of malaria exposure, in collaboration with the United States Army Medical Materiel Development Command (USAMMDA), Naval Medical Research Unit Number 2 (NAMRU-2), Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline (GSK). By evaluation of antibody responses to a large panel of *P. falciparum* and *P. vivax* antigens and multiparameter data analysis; a surrogate marker would allow documentation of malaria exposure in nonimmune individuals without waiting for the appearance of symptoms, and thereby provide a surrogate for placebo control groups in Phase 2 and 3 clinical trials of

antimalarial drugs and vaccines.

Discovery Research - Liver Stage Studies

1. Optimized conditions of in vitro infections of human hepatocytes (HC-04 cell line) with *Plasmodium falciparum* sporozoites in order to develop functional assays for assessing the efficacy of pre-erythrocytic stage malaria vaccines and harvest large quantities of parasite material for transcriptomic and proteomic studies. Different optimizations have been attempted, including expression of CD81 on the host cell and pre-incubation of host cells with a mouse liver homogenate, however, none of these optimizations have produced positive results. Funded by MIDRP.

2. Studies to development the Inhibition of Sporozoite Invasion (ISI) and Inhibition of Liver Stage Development (ILSD) Assays, to more accurately and reproducibly assess the efficacy of pre-erythrocytic stage malaria vaccines in pre-clinical and clinical trials project began at the end of 2006 and will begin full swing in 2007. Funded by MIDRP. Discussions are being conducted with Malaria Vaccine Initiative (MVI) in order to secure funds to become a resource laboratory for these assays as the optimizations progress.

Discovery Research (Vaccine)

1. Evaluation of in vitro Wheat Germ cell-free system for expression of malaria recombinant proteins through a CRADA with the Ehime University, acting through its Cell-Free Science and Technology Research Center. MIDRP funded.

.... a. Screened 159 novel *P. falciparum* genes for protein expression using the Wheat germ cell-free protein expression system developed by our Japanese collaborators at Ehime University and showed that 85% of these proteins were successfully expressed.

.... b. Completed large-scale expression of 7 selected proteins in Japan and brought to NMRC for mice and rabbit immunizations. The protein-specific sera have been used to characterize these antigens. The recombinant proteins are critical reagents for future screening for reactivity to T-cells from volunteers immunized with the irradiated sporozoite vaccine.

2. Awarded Office of Naval Research (ONR) Core Capability Grant to establish this novel Wheat Germ expression system at NMRC and conduct antigen expression and vaccine discovery studies. Wheat Germ expression system has been established to conduct future expression and screening of other malaria vaccine protein candidates.

Antigen Identification

1. Identified 72 highly reactive *P. falciparum* antigens using protein microarrays, in collaboration through CRADA's with University of California Irvine and ImmPort Therapeutics and funding through a SBIR.

2. Designed, constructed and evaluated a protein microarray chip containing sets of

antigens that distinguish between *P. falciparum* clinical cohorts, as well as serodiagnostic antigens from *B. pseudomallei*, *F. tularensis*, *B. burgdorferi* and vaccinia virus. Showed that when probed with sera from infected subjects this multiplex serodiagnostic chip could discriminate between each *P. falciparum* cohort as well subjects infected with each different agent. Done in collaboration through CRADA's with University of California Irvine and ImmPort Therapeutics and funded through a SBIR.

3. Continued application of Transcriptionally Active PCR technology to identify target antigens of protective immunity against malaria from *P. falciparum* genomic sequence data by generating functional PCR fragments for use in in vitro immune screening assays, in collaboration through a CRADA with Gene Therapy Systems and funded by a SBIR.

Pre-Clinical Research

1. Designed, optimized and evaluated the immunogenic capacity of *P. falciparum* bivalent blood-stage adenovirus vectors and trivalent pre-erythrocytic stage vectors, for development of a multi-antigen multi-stage adenovirus based malaria vaccine in collaboration through a CRADA with GenVec and funded by a grant through PATH Malaria Vaccine Initiative (MVI).

2. Generation of multivalent Ad5-*P. falciparum* vaccine vectors. Adenovirus shuttle vectors were constructed to support an MVI-funded collaboration with GenVec through a CRADA.

3. Evaluated vaccinia virus recombinants expressing different forms of *Pf*AMA1 and *Pf*MSP142 funded by MIDRP.

.... a. An immunogenicity study in mice with five vaccinia recombinants expressing different forms of *Pf*MSP142 indicates that the presence or absence of a signal sequence, a GPI anchor sequence and N-linked glycosylation sites can have a dramatic impact on the immunogenicity of vaccinia-*Pf*MSP142 recombinants. Specifically, this study indicated that:

.... (1) Signal sequence enhances the immunogenicity of vaccinia-*Pf*MSP142 recombinants,

.... (2) Replacement of the *Pf*MSP142 GPI anchor sequence with a human GPI anchor sequence, or to a lesser degree, deletion of the *Pf*MSP142 GPI anchor sequence, enhances the immunogenicity of vaccinia-*Pf*MSP142 recombinants and,

.... (3) Modification of the N-linked glycosylation site in *Pf*MSP142 diminishes the immunogenicity of vaccinia-*Pf*MSP142 recombinants.

.... b. An immunogenicity study in mice with three vaccinia recombinants expressing different forms of *Pf*AMA1 indicates that modification of the N-linked glycosylation sites in

*Pf*AMA1 does not have a dramatic impact on the cellular immune responses elicited by these vaccinia-*Pf*AMA1 recombinants.

4. Generated four MVA recombinants expressing *Pf*LSA1, *Pf*SSP2, *Pf*EXP1 and *Pv*AMA1 funded by MIDRP.

5. Identification and evaluation of new vaccine antigens funded by MIDRP.

.... a. Identified the *P. yoelii* orthologues of eight potential vaccine antigens have been.

.... b. Constructed DNA vaccine vectors containing these eight genes.

.. c. Generated Vaccinia recombinants containing six of these genes and have initiated generation of the two remaining recombinants.

6. Designed and evaluated *P. yoelii* pre-erythrocytic stage vectors, to use as proof-of-principle for development of a multi-antigen multi-stage adenovirus based malaria vaccine, through a CRADA with GenVec and funded by an Agile Vaccine Program Grant through the Office of Naval Research (ONR).

7. Evaluated the immunogenicity of *P. falciparum* VEE replicon particle vaccines in mice funded through an Agile Vaccine Program Grant through the Office of Naval Research (ONR).

Preclinical Development

1. *Plasmodium vivax* vaccine development, funded by MIDRP.

.... a. Four antigens (CSP, SSP2, AMA1, MSP1) in three platforms (DNA, Ad5 and replicons), are being tested for their immunogenicity, in both antigen mixing experiments and heterologous prime boost immunizations, using mice. Testing demonstrated that the reagents are immunogenic alone or mixed.

.... b. Blood stage antigens AMA1 and MSP1 in DNA prime-Ad5 boost immunization of *Aotus* monkeys were also tested. The antigens provided partial protection.

2. *Plasmodium falciparum* quantitative PCR, funded by MIDRP.

.... a. Establishing and validating methods to measure malaria parasite burden in blood during clinical trials. We verified our primers, developed a quantitative positive control, and quantitatively analyzed spiked whole blood as a technical proof of the method

3. Conducted safety and toxicity testing in rabbits of a novel multi-stage, multi-antigen adenovector malaria vaccine funded by United States Agency of Infectious Disease (USAID).

4. Conducted disaster check immunogenicity testing in mice of a novel multi-stage,

multi-antigen adenovector malaria vaccine funded by United States Agency of Infectious Disease (USAID).

Clinical Testing

1. Following an Investigative New Drug (IND) allowance by the Food and Drug Administration (FDA), candidate vaccines are tested for safely, immunogenicity and protective efficacy in humans in Phase 1, Phase 2a and Phase 2b clinical trials in the United States and overseas.

.... a. A Two Part Clinical Trial Assessing the Safety, Tolerability, Immunogenicity and Protective Efficacy of NMRC-M3V-Ad-*Pf*CA, a Multivalent, Adenovirus-Vectored *Plasmodium falciparum* Malaria Vaccine, in Healthy, Malaria-Naïve Adults". Funded by: USAID, CDMRP and MIDRP

.... (1) Submitted IND through Sponsor, US Army Surgeon General, on April 2006 and allowed by the FDA for an adenovectored vaccine candidate.

.... (2) Completed multiple IRB reviews.

.... (3) Initiated study October 2006 and is ongoing.

.... (4) Applied for SECNAV designation October 2006 and awaiting response.

.... b. Safety, Tolerability, and Protective Efficacy of a Non-Replicating, Metabolically Active *Plasmodium falciparum* Sporozoite Vaccine (*Pf*-SPZ Vaccine) Administered Subcutaneously, Intramuscularly, or intradermally to Malaria-Naïve Adult Healthy Volunteers. Continued collaboration through a CRADA with Sanaria for clinical testing of a metabolically active *Plasmodium falciparum* sporozoite vaccine.

.... c. Malaria Vaccines: Clinical Research & Trial Sites in Endemic Areas, funded by a NIAID contract through an IAA with NIH and Noguchi Memorial Institute for Medical Research, Accra, Ghana.

.... (1) A Phase 1 Trial of *Pf*CSP DNA/MVA.CSO Prime/Boost Vaccine in Mampong, Ghana. Continued coordination of a multi-national partnership with leading malariologists and epidemiologists in Ghana, the University of Oxford and the National Institutes of Health to sponsor Phase 1 clinical trial of new prime/boost vaccine candidate in Ghana.

.... (2) Established a clinical immunology laboratory capability for testing vaccine responses in human volunteers and then characterized immune responses to *P. falciparum* antigenic targets in Ghanaian adults.

.... (3) Submitted IND through the sponsor NIAID in May 2006 and was allowed June 2006 for the Ghana/MVA trial.

.... (4) Investigators Meeting was held in Ghana in September 2006.

.... d. Understanding the Acquisition, Development, and Maintenance of Protective Immunity to Malaria in Healthy Volunteers by Immunization With Irradiated Sporozoites. Funded by MIDRP

.... (1) Established collaborations with WRAIR for affymetrix gene chip analysis, and Sun Biomedical Technologies, Inc., Riverside, CA for SELD-TOF analysis.

.... (2) Continued protocol development under new Principal Investigator.

OCONUS Collaborations

1. Continued to work closely with (NAMRU-3's) Ghana Detachment, including Noguchi Memorial Institute for Medical Research, Navrongo Health Research Center, and Kintampo Health Research Center.

.... a. Principal collaborative efforts have been to bring the new clinical laboratory at Noguchi up to high standards as assessed by CAP (College of American Pathologists) periodic testing.

.... b. Performed data analysis on DoD# NAMRU3.2002.0008 (The dynamics of severe anemia and malaria parasitemia in young children during the high transmission season in Northern Ghana)

.... c. Coordinated and provided GLP training and certification at both Noguchi Memorial Institute for Medical Research and Navrongo Health Research Center.

2. Consultant duties continue for a WHO-funded project established at NAMRU-3 for molecular genotyping of parasite (*P. falciparum*) DNA from various sites in Africa and Western Asia conducting in vivo tests for resistance to antimalarial drugs.

3. Collaborations continue with NMRCD in Lima, Peru, to develop a stable laboratory colony of *Anopheles albimanus* for use in *P.vivax* challenge trials.

4. Collaborations continue Dr Socrates Herrera and Dr Miriam Herrera at the Malaria Vaccine and Drug Testing Center in Cali, Colombia, in order to facilitate a human challenge at NMRC with Colombian *Anopheles* infected with *P. vivax*.

IOM Review

1. The DoD Malaria Vaccine Program consisting of the programs from WRAIR and NMRC underwent a solicited review by the Institute of Medicine in January 2006 coordinated through USAMRMC and MIDRP.

.... a. Recommendations from that review were published in “Battling Malaria: Strengthening the US Military Malaria Vaccine Program.” Committee on US Military

Malaria Vaccine Research: A Program Review, Medical Follow-up Agency, The Institutes of Medicine of the National Academies, Gaves, PM and Levine, MM Editors, The National Academies Press, Washington DC, 2006.

.... (1) Part of the recommendations included a Scientific Advisory Board which was assembled and convened in November 2006 to review in programs scientific programs and provide guidance on planning and prioritizing projects.

.... b. Further recommendations to follow at the beginning of 2007.

Patents within the Malaria Program

NC 97631 – US Patent Application No. 60/713,110
Adenoviral Vector-Based Malaria Vaccines (Prosecuted and paid for by Gen Vec, Inc.)
Filed Non-provisional Application on 31 Augusts 2006
Filed PCT on 31 August 2006
Updated PRV Status on 30 September 2006

NC 97632 – US Patent Application No. 11/513,439
Malaria Antigen Screening Method
Non-Provisional Filed on 28 August 2006
PCT Filed on 28 August 2006
Updated PRV Status on 28 August 2006

Bone Marrow Research Directorate (05)

The Bone Marrow Research (Registry) Directorate of the Naval Medical Research Center operates the C. W. Bill Young Marrow Donor Recruitment and Research Program, the Department of Defense Marrow Donor Program. The purpose of the program is to perform research, development, test and evaluation for medical countermeasures for marrow toxic exposures and for unrelated donor “marrow” transplantation. The program initiated federal support for the National Marrow Donor Program and today provides support and oversight for the National Marrow Donor Program and the DoD program to recruit volunteer donors throughout DoD under a Policy of the Assistant Secretary of Defense (Health Affairs) and performs research to improve the science and technology of transplant matching and other technologies important to improving unrelated donor “marrow” transplantation. These national resources and medical technology used daily to treat patients are available in the event of ionizing radiation or chemical toxic exposure.

The Navy/DoD has recruited over 400,000 volunteers from DoD (over 35,000 in this reporting period); provided marrow from over 370 volunteers; provided critical research and development on HLA testing; identified over 80 new HLA alleles; identified new approaches and over 10 alleles of the KIR antigen series, and provided extensive

technology leadership in developing CLIA approved HLA testing for marrow transplantation.

The NMDP consists of 6,400,000 volunteer donors; one coordinating center in Minneapolis; 75 donor centers; 166 “marrow” transplant centers; 188 “marrow and PBSC (peripheral blood stem cell (cells containing the same adult “marrow” stem cell as marrow)) collection centers; 21 cord blood banks with 53,000 cord bloods; and 20 HLA testing laboratories.

Supported over 370 DoD volunteer donors to provide marrow for patients needing a transplant to save their life. (Over 2,000 total donations from DoD volunteers since the beginning of the program)

Assisted the National Marrow Donor Program to provide 3,300 marrow and PBSC donations from volunteers. (Over 26,000 donations through the NMDP since the start of the program.)

Recruited over 35,000 new DoD volunteers for the DoD and National Marrow Donor Program Registry, performed intermediate resolution DNA based HLA (Human Leukocyte Antigen) typing using the Luminex fluorescence bead-oligonucleotide probe technique and added their HLA type and demographics (without personal identifiers) to the National Marrow Donor Program Registry.

Supported the National Marrow Donor Program to recruit and add to the NMDP Registry 400,000 new volunteer donors.

Worked within the DoD Program, the Department of Health and Human Services, Health Resources and Services Administration (HRSA), DHHS emergency Preparedness

Program, and National Marrow Donor Program to refine the medical contingency response for marrow toxic injury caused by ionizing radiation or chemical weapons containing mustard.

Continued to improve the specificity of the intermediate resolution Luminex fluorescence bead SSOP (sequence specific oligonucleotide probe) technique.

Because of the technology improvements the per sample cost of HLA testing by the Luminex method, per sample costs were reduced by 10% and this reduction in cost was also realized by the NMDP in its contracts with HLA testing laboratories.

The improvements in HLA resolution and simultaneous cost reduction are critical to the underlying goal of developing the capability of finding a very well matched donor (7 of 8 or 8 of 8 allele matched for HLA-A,B,C and DR) for every patient searching.

To achieve the ability to find donors for all patients, national donor recruitment will need to be increased. Increased donor recruitment is one of the NMDP goals required by the NMDP Board of Directors with HHS and Navy concurrence. The Navy has played a key

role in instituting policies and operations to increase donor recruitment through out the National Marrow Donor Program.

Continue to improve DNA sequencing methodology for HLA testing to assure robust results and improved allele specificity primarily through re-analysis of DNA sequence information on all known HLA types for HLA-A, HLA-B, HLA-C, and HLA-DRB1, identifying new allele specific primers for secondary DNA amplification and testing and validating the modifications.

Reported over 80 new HLA alleles (GeneBank, International HLA nomenclature committee, publications).

Modified the HLA test manual for the laboratory for both SSOP and sequence based testing.

Passed biennial CLIA (clinical laboratory improvement amendment) self inspection and certification (alternate years on site inspection and self inspection with formal report to inspecting agency.)
Assisted the NMDP implement an new computer based analytic system to support transplant centers to identify the most likely match for each patient from among over 6,400,000 potentially matched volunteer donors listed on the NMDP file. Because this analytic and reporting system, patients can find the correct donor more quickly and significantly fewer potentially matched donors identified during the search need to be retested at allele level to find the correct match.

This analytic system is a revolutionary change, making unrelated donor transplantation practical for an increasing number of searching patients.

Had a national conference of DoD marrow donor recruiters.

Continued to implement the new regional donor recruitment volunteer support structure for DoD donor recruitment.

Refined approaches to utilize the buccal swabs sample method in place of blood for donor sample acquisition in place of blood. The use of buccal swabs to obtain DNA material for genetic testing is very important to increasing donor recruitment and donor drives are simplified.

Continued to work closely with the Department of Health and Human Services, HRSA (Health Resources and Services Administration) to assist oversight of the National Marrow donor Program operations. Assisted HRSA evaluate a restructuring of the national system for unrelated donor transplantation, named the C. W. Bill Young Cell Transplantation Program. The structure now includes increased support for cord blood banks, increased support for cord blood transplantation, continued programs for adult marrow and PBSD donation, increased support for patients, and increased emphasis on transplant outcome evaluation and system wide emphasis in developing both improved

standard clinical transplant methods and evaluation of novel approaches to clinical transplantation.

Continued to work with National Institutes of Health intramural programs (NCI, NIAID and laboratory medicine) to develop a program for intramural clinical transplantation research for unrelated donor marrow, PBSC, and cord blood transplantation.

Biologic Defense Research Directorate (06)

Immunology and Hand Held Assay Department

During the past year the Immunology and Hand Held Assay Department has continued to develop assays and antibodies for Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) and the Defense Threat Reduction Agency (DTRA). The Immunology Department is currently working in the BDRD Annex in Rockville as well as at the WRAIR/NMRC building. The group has produced over 1.2 kg of antibody for the JPEO-CBD this year and 20,000 hand held assays. The Immunology Department continues to function as the Conformance Test Laboratory for all DoD antibodies available through the Critical Reagents Program. In addition, the Immunology Department has continued to develop improved immunological reagents using the mass spectroscopy facility that was funded by DTRA in 2005. DTRA continued to fund these efforts in 2006. During 2006, the Immunology Department obtained additional DTRA funding to develop and test immunoassays on two new platforms that have great potential for fielding. These platforms may give the DoD the ability to field more sensitive assays without an increase in assay time.

Molecular Diagnostics Department

Throughout CY06, the Molecular Diagnostics department has continued to provide support of the Fleet's biological detection capabilities. In CY03, the department completed an initial program of outfitting all the large deck ships in the Fleet with instruments, reagents, and trained personnel. The department continues to outfit ships,

produce reagents kits, conduct shipboard site visits, and oversee a quality control (QC) program to maintain the operational readiness of the Fleet's instruments and personnel. Monthly QC checks keep the shipboard personnel proficient in the protocols and techniques necessary for the Fleet's biological detection capabilities. BDRD continues to train new personnel through the Fleet Biological Warfare Detection course. In CY06, the shipboard detection capability was enhanced by the addition of reagents of two additional biological agents. This was required to mirror the immunological assays of the Joint Biological Point Detection System (JBPDS) units recently installed on select ships. The department has continued a program of assay development during CY06 to expand the range of assays currently fielded. Assays for new agents and additional targets for the prioritized list of agents have been developed based on the proven probe hydrolysis method of reporting. Efforts toward multiplexing assays to detect several targets for a single agent or multiple agents simultaneously have been successful. Multiplexed assays decrease the time and reagents needed to test for a more diverse set of targets thereby increasing the speed and efficiency of sample analysis. Additionally, new

assays were developed for use with pyrosequencing instrumentation. Pyrosequencing is a real-time method of sequencing short stretches of DNA and allows absolute identification of agents such as Bacillus anthracis, Yersinia pestis, and smallpox that have high sequence similarity to non-target organisms. Previously developed probe hydrolysis assays have continued to be transitioned to the Nanogen Microelectronic Array. In CY06 assays have been successfully transitioned and multiplexed for this platform using the probe down format in contrast to the amplicon down format previously employed. It is anticipated that as more assays are transitioned, a capability to test large numbers of samples for a number of high priority agents will be developed. The department has continued to participate in sample analysis for multiple federal agencies, such as the FBI, DHS, and US Secret Service, within the National Capitol Region.

Operations Department

During CY06, the Operations Department continued to support Fleet Forces Command in operation of the Fleet PCR-based biological confirmation capability through the conduct of shipboard site visits and presenting briefings to Fleet Forces Command, the Fleet Heath Domain Board of Directors Meeting, and other operational medicine functions. As the performing activity POC for the Fleet Program MIPR, the department continues to provide oversight of student registration, staffing for the Fleet Biological Warfare Detection course, and execution of funds. The department continued to assist the Fleet Forces Command, Naval Surface Warfare Center – Dahlgren Laboratory, and the Bureau of Medicine and Surgery assess the Joint Biological Agent Identification and Diagnostics System for naval utility. Throughout CY06, the Operations Department continued to enhance its mobile biological agent detection and identification laboratories in terms of equipment, protocols and concept of operations. The objective is to increase capability while reducing weight/cube footprint. The department worked with the Immunology Department to test and evaluate a new immunological platform with efforts directed towards adding multiplexed assays for the top 10 biological threat agents to the deployable laboratory. An ongoing assessment of portable glove boxes will increase the safety of personnel assigned to one of the Biological Agent Identification and Confirmation Teams (BAICT). The mobile BAICT performed field exercises at Fort Indian Town Gap, PA and Dugway Proving Grounds – Joint Operational Testing and Training Center, UT. The departments Biological Safety Level 3 laboratory continued to

produce research results and antigens for other BDRD departments. The department has continued to participate as subject matter experts for multiple DoD organizations, including the Bureau of Medicine and Surgery, Fleet Forces Command, Naval Surface Warfare Center, Navy Warfare Development Command, Chemical Biological Incidence Response Force - II Marine Expeditionary Force, US Special Operations Command, and the Defense Intelligence Agency.

Vaccine Department

DNA vaccine for anthrax: The department focuses on developing DNA based vaccines to protect the warfighter against bio-threat agents such as anthrax. We have continued to build on the success of the human phase I clinical trial recently completed by a collaborator using plasmids we developed by developing newer version of this vaccine capable of conferring rapid protection in the shortest possible time.

Multi-agent vaccine development: We have actively pursued the development of DNA based vaccines capable of conferring rapid protection against multiple select agent threats. With funding from DTRA we have been able to develop a formulation capable of conferring protection against a lethal aerosol challenge with Y.pestis, the causative agent of plague. Results demonstrating the utility of this approach for anthrax will be available by the end of FY07.

Our efforts to develop viral vectors with similar efficacy are continuing via a collaboration with researchers based at the US Army Medical Research Institute of Infectious Disease, Ft Detrick, MD. The first prototype vectors will be tested in the summer of 2007. In addition we have identified two potential vaccine targets for a third bacterial threat agent, Burkeholderia pseudomallei, the causative agent of melioidosis, and have confirmed their ability, in animal models, to confer protection against this organism. Work is in progress to incorporate all of these elements into a trivalent vaccine.

Innate stimulators of protection: The ability to stimulate broad spectrum protection against a range of potential warfare agents would offer considerable operational advantages to the commander in the field. The human immune system possesses a specialized 'early warning system' in the form of a panel of detectors to rapidly sense and trigger responses to the presence of microbial invaders. With DTRA funding we have developed cell based reporter systems and used them to study how known innate stimulators, primarily agonists of TLR7 and TLR9, stimulate immune specific responses. Studies are in progress to determine the ability of these stimulators to confer direct protection against live agent challenge and to enhance vaccine induced adaptive immune responses.

Plant based expression systems: Our efforts to develop plant based expression systems for the production of human monoclonal antibodies and as oral vaccines against bio-threat agents have continued.

Therapeutic human monoclonal antibodies: We are continuing to develop therapeutic antibodies for anthrax and are currently investigating the feasibility of administering them with vaccine candidates. Hybridoma's expression antibodies against botulinum

neurotoxin A have been isolated and are in the process of being assessed for efficacy. Work is in progress to identify the epitopes recognized by murine protective monoclonal antibodies which target the plague vaccine proteins, F1 and LcrV.

The major success of the year included:

- Combined anthrax/plague DNA vaccine demonstrated efficacy
- Identified human monoclonal antibodies for the treatment of botulinum type A neurotoxin
- Four new medical countermeasure programs funded by DTRA
- Established a second collaborative effort with researchers at USAMRIID
- Two new CRADA's

Genomics Group

In 2006 the BDRD Genomics group continued to consolidate its technology and manpower base. At the end of the year the group had 12 members in its location at the annex at 12300 Washington Avenue, Rockville. Key equipment included two Roche/454 GS20 sequencers, Affymetrix and Nimblegen array technology, a Maui 12 chamber hybridization system, two Beckman Biomek FX robots and an Apple Xserve cluster. The group expanded its de novo bacterial genome sequencing efforts completed six high quality sequences of biodefense agent Burkholderia and four of Yersinia. The 454 sequencer was also used for several other sequencing projects. For its resequencing operations, designs for several biodefense resequencing arrays were completed including Yersinia pestis and Brucella suis. A large effort into verifying single nucleotide polymorphisms in Francisella tularensis using Nimblegen resequencing was also in progress during 2006. Work led by Dr Shanmuga Sozhammanan resulted in a new bacteriophage lambda vector for vaccine target expression. Additionally a large proteomic based Bacillus spore vaccine project revealed a number of conserved Bacillus spore vaccine targets.

2006 was a landmark year for Genomics group funding. Dr Read was a awarded a $15M 3 year project from the DOD TMTI (Translational Medical Technologies Initiative) program through DTRA for his project entitled “Digital Strain Collections for the TMTI: High-throughput genomic sequencing of worldwide pathogen and non-pathogenic (P/N-P) near-neighbor bacterial strains, phenotypic screening and development of bioinformatic analysis methods”. Dr Sozhammanan and Dr Read received funding from the DTRA Joint Science and Technology Office (JSTO) program entitled “Rapid Discovery of Small Molecule Antimicrobials Through Bacteriophage Genomics”

These funded programs supplemented the four existing DTRA awards to the Genomics group running through Fiscal Year 2006/2007.

Dr Read presented an informal summary of the Genomics Group activities to the NMRC Infectious Diseases Directorate.

Resource Management Directorate (07)
Finance and Budget Department

Resource Directorate staff assists the Director in support of budget and accounting tracking commitments and obligations, processing of approved travel requests, development of support agreements, MOU’s, MOA’s, Military Interdepartmental Purchase Requests, Work Requests, and to ensure quality materiel and support services are provided to customers in a timely manner and at a competitive costs. The Directorate consists of three Departments: Finance and Budget, Travel, and Materiel Management.

Head: Cheryl Carr

The Finance and Budget Department focuses on delivering quality financial services in a timely manner at a competitive cost. Responsible for the development of and execution

of operating budgets and reimbursable orders issued to NMRC and subordinate commands. Financial management services to include budget, accounting, reimbursables, and defense regional interservice support for NMRC and subordinate laboratories.

- As NMRC was named R&D medical headquarters effective early 2006, a transition period to identify functions and additional responsibilities for each section was established.

- In support of new responsibility for five other commands, the Finance and Budget department a headquarters section was created assuming headquarters function.

- Financial staff worked with BUMED, NMSC, NHRC, and DFAS, Charleston, to develop chargeable UICs in the official accounting system. The chargeable UICs were established and ready for use by the new fiscal year.

- Developed and implemented a process to outlay the flow of documents throughout the commands in preparation of FY07 fiscal year.

- The project of all ten laboratories utilizing the NMRC Financial Planning System and the planned disestablishment of the NHRC's financial tool STARGATE did not meet the 1 OCT 2006 deadline due to technical issues. Technical issues have been resolved and project is expected to be fully operational for all ten laboratories by the 1 APR 2007 deadline imposed by Naval Medical Support Command. This system will provide all customers with a web based status of funds and activity management tool that is real time and based on official accounting system.

- Current efforts focus on the improved performance to meet the financial benchmarks.

- Implemented new procedures to reduce the volume of unmatched disbursements as well as reducing the number of undelivered orders in the prior years.

Travel Department

Manager: Eric Campbell

The travel office is dedicated to supporting the scientific and military goals of the command. The staff strives to continually recognize the needs of our travelers and procedurally improve the service to meet the needs. Provide efficient, knowledgeable, accurate, and timely service making the travel process simple and convenient.

- New procedures implemented continue to improve the quality of service provided through DTS system.

- Improvements made to the travel section web page available on the command homepage. Instructions, forms that can be filled out from the desktop and other helpful links are provided to assist the traveler.

- Worked with BUMED to prepare new hierarchal system for FY07. NHRC labs line of accounting can be viewed by the travel staff.

- NMRC travel staffer traveled to NIDBR to assist in setting up their command's DTS program and provide additional guidance to NIDBR travel department.

Materiel Management Department

Manager: LT Eugene Osborn

The mission of the Materiel Management Department is to ensure quality material and support services are provided to customers in a timely manner and at a competitive cost. The department is responsible for logistic and property management for the command to include: the ordering, receiving, inspecting and distributing requested materials; maintaining management liaison with the Material Management Department NNMC, Bethesda and with the Walter Reed Army Institute of Research (WRAIR). Policies are implemented pertaining to equipment management constituting contracting, purchasing, receipt, inventory control maintenance and repair.

- Established updated informational web page available on command's homepage.

Plant Property

Controls all material receipts, property management functions to include: inspections (inventories), equipment accounting, equipment surveys/disposal, transfer and equipment loan program, and maintenance of an equipment inventory database annotating current ownership and locations.

- Responsible for oversight and inventory of enterprise wide equipment inventory.

Contracting

Reviews Statements of Work, monitors maintenance contracts and drafts contract modifications. Responsible for all purchasing actions requiring issuance of Purchase

and Delivery Orders and credit card purchases for those departments without credit card authority. Act as the sole source of coordination with vendors on behalf of other directorates, activities with NMRC and tenant commands. Monitor and implement all Service Contracts with the command. This branch assists the Department Head of Materiel's Management in planning, developing, implementing and administering NMRC's contracting program.

- Command has had the GS-12 contracting officer position vacant for over a year. This vacancy has impacted the workload of several employees and the command has had to rely more often on NNMC contracting assistance.

Bio-Medical Repair

This technician provides maintenance/prevention maintenance, repair of equipment safety inspections of equipment and maintenance of a database (BIOFACs) to ensure adequate planning for equipment modernizations programs.

- Coordinate with NMLC to replace outdated BIOFACs with DMLSS

- Successful in coordinating successful inspection, certification and repairs of hoods located at NMRC campuses

Receipt Control

Oversees command credit card program, reconcile and certifies command credit card statements and vendor invoices for payment. Liaisons with DFAS Charleston and DFAS San Diego to address billing problems, maintains acquisition tracking database and responds to customer service inquiries and customer service support. Manage the Government Wide Purchase Card Program (GPC). Authority to use the GCPC for procurement actions not to exceed $2,500 has been delegated to the department level activities at NMRC. The Contracting Branch will procure items for those departments not in possession of GPC.

- As a headquarters inherited oversight responsibility for all ten laboratory purchase card programs. Developing procedures based on guidance from NMSC and BUMED to reduce frequency delinquent listing.

- LT Osborn responsible to track progress of ten laboratories.

- Staff shortage has affected the frequency of the NMRC purchase card delinquency. Corrective measures taken to resolve the situation

- Developed tracking system to show what orders were assigned to which purchasing agent. Assists with queries from customers and tracking down completed orders.

Shipping & Receiving

Responsible for receiving, shipping, delivery, and coordination of the materiel bulk storage for NMRC, and its tenant commands. All material shipped to NMRC is processed for verification/validation, temporary secure storage, and ultimate delivery to customers.

The short narrative should amplify chronology entries (such as objectives and results of exercises/ operations; commander's evaluation of exercises/operations, etc). Entries may refer to an enclosure of this report without additional description if the enclosure sufficiently reports the incident/event. For all other entries, give the date or period in YYYY-MM-DD format and provide a brief narrative. All significant events during the reporting period are to be included.

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## 4. Supporting Reports

Supporting Reports are those reports required by other instructions that provide significant data about the command during the calendar year. These reports may be submitted "as is," eliminating the need to duplicate information for this report that is already contained in reports prepared in response to other instructions and requirements. Examples include battle efficiency, safety and other award submissions, major staff or command studies, and end of cruise reports or briefs. For units engaged in or directly supporting combat, significant wartime or peacetime operations (named operations, non-combat evacuation operations, disaster relief or other humanitarian operations, etc.) or major exercises, enclosures may include, but are not limited to:

a. Situation Reports
b. Intentions Messages
c. Operational Reports
d. Operations Orders/Deployment Orders
e. Operational Plans
f. Personal For Messages
g. After Action Reports
h. Significant Electronic Message Traffic (outgoing/e-mail/chat)
i. Battle Damage Assessments
j. Casualty Reports
k. End-of-Cruse/Deployment Reports
l. Intelligence Summaries
m. Major Exercise Reports

List below the items submitted, indicating the classification of each. Electronic reports should be in a Microsoft Office format (Word, Excel, Power Point, or Access), HTML, PDF, JPG, GIF, or plain text. It is unnecessary to convert non-electronic documents to electronic format. Submit electronic reports via e-mail or on CD-ROM as explained at the end of this form. Enclosures that do not exist in electronic format should be listed below and submitted in hardcopy in the same manner as a CD-ROM.

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## 5. Published Documents

List below the published documents being submitted in either electronic or paper format, indicating the classification of each item. Documents to be submitted include cruise books, change of command programs, commissioning/decommissioning brochures, establishment/disestablishment/deactivation brochures, copy of command's web site, news releases, biography of commander, welcome aboard brochures, newspaper articles, command studies, statistical data, etc.

Electronic documents should be in a Microsoft Office format (Word, Excel, Power Point, or Access), HTML, PDF, JPG, GIF or plain text. Documents in electronic format are to be submitted via e-mail or on CD-ROM as explained at the end of this form. It is unnecessary to convert non-electronic documents to electronic format. List any enclosures that are not electronic and submit in hardcopy in the same manner as a CD-ROM.

As a part of this report, NMRC submits:
Attachment (1) Biography of the Commanding Officer (.doc format)
Attachment (2) Biography of the Executive Officer (.doc format)
Attachment (3) Change of Command program (.pdf format)

In addition, following is a list of the abstracts, publications, and presentations during the reporting period by Directorate:

Administration Directorate (01)

Research Services Directorate (02)

Publications:

1. Cox JD, Taylor K. Whistleblower woes: lack of support. Lab Animal. 2006 Mar; 35(3):16-7.

2. Johnson T, Arnaud F, Dong F, Philbin N, Rice J, Asher L, Arrisueno M, Warndorf M, Gurney J, McGwin G, Kaplan L, Flournoy WS, Apple FS, Pearce LB, Ahlers S, McCarron R, Freilich D. Bovine polymerized hemoglobin (hemoglobin-based oxygen carrier-201) resuscitation in three swine models of hemorrhagic shock with militarily relevant delayed evacuation-Effects on histopathology and organ function. Critical Care Medicine. 2006 May; 34(5):1464-74.

3. Shelton LJ, White CE, Felt SA. A comparison of non-contact, subcutaneous, and rectal temperatures in captive owl monkeys (Aotus sp.). Journal of Medical Primatology. 2006 Dec; 35(6):346-51.

Combat Casualty Care Directorate (03)

Publications:

1. Arnaud F, Handrigan M, Hammett M, Philbin N, Rice J, Dong F, Pearce LB, McCarron R, Freilich D. Coagulation patterns following haemoglobin-based oxygen carrier resuscitation in severe uncontrolled haemorrhagic shock in swine. Transfusion Medicine. 2006 Aug; 16(4):290-302.

2. Bullock MR, Mahon R. Hypoxia and traumatic brain injury - Response. Journal of Neurosurgery. 2006 Jan; 104(1):171-2.

3. Chavko M, McCarron RM. Extension of brain tolerance to hyperbaric O(2) by intermittent air breaks is related to the time of CBF increase. Brain Research. 2006 Apr 21; 1084(1):196-201.

4. Chavko M, Prusaczyk WK, McCarron RM. Lung injury and recovery after exposure to blast overpressure. Journal of Trauma. 2006 Oct; 61(4):933-42.

5. Crane NJ, Kansal NS, Dhanani N, Alemozaffar M, Kirk AD, Pinto PA, Elster EA, Huffman SW, Levin IW. Visual enhancement of laparoscopic nephrectomies using the 3-CCD camera. In: FS Azar; DN Metaxas, editors. Multimodal Biomedical Imaging, (Proceedings of SPIE, vol. 6081). Bellingham, Wash.: SPIE, 2006.

6. Dainer H, Nelson J, Brass K, Montcalm-Smith E, Mahon R. Short oxygen pre-breathe and intravenous perfluorocarbon emulsion reduces morbidity and mortality in a swine saturation model of decompression sickness. Journal of Applied Physiology. 2006:[Epub ahead of print Nov 9].

7. Dong F, Hall CH, Golech SA, Philbin NB, Rice JP, Gurney J, Arnaud FG, Hammett M, Ma X, Flournoy WS, Hong J, Kaplan LJ, Pearce LB, McGwin G, Ahlers S, McCarron R, Freilich D. Immune effects of resuscitation with HBOC-201, a hemoglobin-based oxygen carrier, in swine with moderately severe hemorrhagic shock from controlled hemorrhage. Shock. 2006 Jan; 25(1):50-5.

8. Fahlman A, Dromsky DM. Dehydration effects on the risk of severe decompression sickness in a swine model. Aviation Space and Environmental Medicine. 2006 Feb; 77(2):102-6.

9. Fahlman A, Kayar SR. Nitrogen load in rats exposed to 8 ATA from 10-35 degrees C does not influence decompression sickness risk. Aviation Space and Environmental Medicine. 2006 Aug; 77(8):795-800.

10. Johnson T, Arnaud F, Dong F, Philbin N, Rice J, Asher L, Arrisueno M, Warndorf M, Gurney J, McGwin G, Kaplan L, Flournoy WS, Apple FS, Pearce LB, Ahlers S, McCarron R, Freilich D. Bovine polymerized hemoglobin (hemoglobin-based oxygen carrier-201) resuscitation in three swine models of hemorrhagic shock with militarily relevant delayed evacuation-Effects on histopathology and organ function. Critical Care Medicine. 2006 May; 34(5):1464-74.

11. Kaplan LJ, Philbin N, Arnaud F, Rice J, Dong F, Freilich D. Resuscitation from hemorrhagic shock: fluid selection and infusion strategy drives unmeasured ion genesis. Journal of Trauma. 2006 Jul; 61(1):90-7; discussion 7-8.

12. Ludwig BB, Mahon RT, Schwartzman EL. Cardiopulmonary function after recovery from swimming-induced pulmonary edema. Clinical Journal of Sport Medicine. 2006 Jul; 16(4):348-51.

13. Mahon RT, Dainer HM, Nelson JW. Decompression sickness in a swine model: isobaric denitrogenation and perfluorocarbon at depth. Aviation Space and Environmental Medicine. 2006 Jan; 77(1):8-12.

14. McCarron RM, Chen Y, Tomori T, Strasser A, Mechoulam R, Shohami E, Spatz M. Endothelial-mediated regulation of cerebral microcirculation. Journal of Physiology and Pharmacology. 2006 Nov; 57 Suppl 11:133-44.

15. Pearl JP, McNally MP, Elster EA, DeNobile JW. Benign pneumoperitoneum after colonoscopy: a prospective pilot study. Military Medicine. 2006 Jul; 171(7):648-9.

16. Rice J, Philbin N, Handrigan M, Hall C, McGwin G, Ahlers S, Pearce LB, Arnaud F, McCarron R, Freilich D. Vasoactivity of bovine polymerized hemoglobin (HBOC-201) in swine with traumatic hemorrhagic shock with and without brain injury. Journal of Trauma. 2006 Nov; 61(5):1085-99.

17. Rice J, Philbin N, McGwin G, Arnaud F, Johnson T, Flournoy WS, Pearce LB, McCarron R, Kaplan L, Handrigan M, Freilich D. Bovine polymerized hemoglobin versus hextend resuscitation in a swine model of severe controlled hemorrhagic shock with delay to definitive care. Shock. 2006 Sep; 26(3):302-10.

18. Steinberg JS, Stojadinovic A, Elster E, Peoples G, Attinger CE. Is there a role for ESWT in wound care? Podiatry Today. 2006 Jul; 19(7):62-8.

Presentations:

1. Alemozaffar M, Gorbach A, Kansal NS, Dhanani N, Gage F, Kirk A, Elster E, Pinto P. Intraoperative uretal identification with infrared imaging. Western Section, American Urological Association Meeting, Maui, Hawaii, October 22-27, 2006.

2. Alemozaffar M, Gorbach A, Kansal NS, Dhanani N, Gage F, Kirk A, Elster E, Pinto P. Intraoperative infrared imaging to assess renal reperfusion for renal transplantation. Western Section, American Urological Association Meeting, Maui, Hawaii, October 22-27, 2006.

3. Arnaud F, Philbin N, Rice J, Dong F, McCarron R, Freilich D. Coagulation parameters after fluid resuscitation in severe hemorrhage and brain injury. 35th Critical Care Congress, San Francisco, CA, January 7-11, 2006. Abstract no. 150-S.

4. Arnaud F, Tomori T, McKeague A, Prusaczyk K, McCarron R. Comparative evaluation of hemostatic agents for first responders. Advanced Technology Applications for Combat Casualty Care, St. Pete Beach, Florida, August 13-17, 2006.

5. Arnaud F, Tomori T, Saito R, McCarron RM, Nicholson CE. Predictors for survival in a fast bleed hemorrhage model. 35th Critical Care Congress, San Francisco, CA, January 7-11, 2006.

6. Chavko M, McCarron RM, Prusaczyk WK. (Poster). Progression of oxidative and inflammatory injury in the lung after exposure to blast overpressure. Experimental Biology 2006, San Francisco, CA, April 1-5, 2006. Abstract No. LB547.

7. Crane N, Hale D, Pinto P, Gage F, Tadaki D, Levin I, Kirk A, Elster E. (Poster). Pneumoperitoneum has no effect on tissue oxygenation during laparoscopic donor nephrectomy using visible light collection by the 3-CCD camera. World Transplant Congress, Boston, MA, July 22-27, 2006. Abstract No. 2236.

8. Crane N, Hale D, Pinto P, Gage F, Tadaki D, Kirk AD, Levin I, Elster E. (Oral Presentation). Non-invasive renal vessel differentiation during laparoscopic donor nephrectomies. World Transplant Congress, Boston, MA, July 22-27, 2006. Abstract No. 1135.

9. Dainer H, Soutiere S, Mahon R. Accelerated decompression following saturation at 5 ATA: initial success of an aggressive rescue profile using oxygen prebreathe. Undersea & Hyperbaric Medical Society Annual Meeting, Orlando, FL, June 22-24, 2006.

10. Davis TA, Gage F. Maximal cord blood recovery and CD34+ progenitor cell collection using machine pulsatile perfusion of placentas. 48th American Society of Hematology Annual Meeting, Orlando, FL, December 9-12, 2006. 48th American Society of Hematology Annual Meeting: Program and Abstracts. Abstract No. 3643.

11. Elster E, Gorbach A, Tadaki D, Gage F, Pinto P, Kirk A. Intraoperative assessment of reperfusion of renal transplants. World Transplant Congress, Boston, MA, July 22-27, 2006.

12. Elster E, Gage F, Tadaki D, Hale D, Leeser D, Fernandez C, Destephano D, Kirk A, Gorbach A. (Poster). Infrared imaging of cadaveric organ viability with pulsatile perfusion. World Transplant Congress, Boston, MA, July 22-27, 2006. Abstract No. 2589.

13. Elster E. Trauma and immune response: strategies for success. 12th Annual San Antonio Trauma Symposium, September 18-21, 2006.

14. Elster E, Hanna B, Agrawal S, Gage F, Jannu S, Kirk A, Eledath J, Gorbach A. Real time identification of critical surgical structures using image fusion. World Transplant Congress, Boston, MA, July 22-27, 2006.

15. Gage F, Gorbach A, Hale D, Tadaki D, Leeser D, Fernandez C, DeStephano D, Kirk A, Wang H, Elster E. (Poster). Assessment of pharmacologic resuscitation during

pulsatile perfusion. World Transplant Congress, Boston, MA, July 22-27, 2006. Abstract No. 2590.

16. Goddard J, Gee T, Wang H, Gorbach A. (Oral presentation). Segmentation-based registration of organs in intraoperative video sequences. 2nd International Symposium on Visual Computing, Lake Tahoe, Nevada, November 6-8, 2006.

17. Gorbach A, Wang H, Alemozaffar M, Dhanani N, Gage F, Kirk A, Pinto P, Smith P, Elster E. Intraoperative imaging to assess organ viability: from bed to bench side. NIH Optical Imaging Meeting 2006, NIH, Bethesda, MD, September 25-27, 2006.

18. Landauer MR, Clarke TK, Mogg S, Davis T. Radioprotection by Genistein: enhancement of survival and hematopoietic recovery in lethally irradiated mice. 53rd Annual Meeting of the Radiation Research Society, Philadelphia, PA, November 6-9, 2006.

19. Leeser DB, Abbott KC, Elster E, Swanson SJ, Bohen E, Yuan C, Oliver JD. (Poster). Graft survival in African American recipients with equal access to care is comparable to non-blacks at 3 and 5 years but worsens at 10 years. World Transplant Congress, Boston, MA, July 22-27, 2006. Abstract No. 1818.

20. McCarron RM, Chen Y, Tomori T, Spatz M. Brain microvascular function: role of endothelium in the regulation of cerebral microcirculation and blood-brain barrier. XXIII Congress of Polish Physiological Society: Physiology Without Limits Warsaw, Poland, September 14-16, 2006. Journal of Physiology and Pharmacology. 2006 Sep; 57(Suppl 2):52.

21. McKeague A, Arnaud F, Tomori T, Prusaczyk K, McCarron R, Currier S, Kharod C. Evaluation of novel formulations of zeolite hemostatic agent (QuikClot). Advanced Technology Applications for Combat Casualty Care, St. Pete Beach, Florida, August 13-17, 2006.

22. Montcalm-Smith EA, Caviness J, Chen Y, McCarron R. Stress biomarkers in a rat model of decompression sickness. Undersea & Hyperbaric Medical Society Annual Meeting, Orlando, FL, June 22-24, 2006.

23. Philbin N, Rice J, McNickle K, Williams R, Warndorf M, Arnaud F, McCarron R, Freilich D. HBOC-201 resuscitation in a swine model of severe controlled hemorrhage with 24-hour delay to hospital-like care. 35th Critical Care Congress, San Francisco, CA, January 7-11, 2006. A35.

24. Rice J, Stern S, Philbin N, Johnson T, Szabo K, McGwin G, Arnaud F, Flournoy S, McCarron R, Freilich D. Resuscitation with HBOC-201 vs. Lactated Ringer's (LR) following severe uncontrolled hemorrhage and concomitant traumatic brain injury (TBI) in swine. 35th Critical Care Congress, San Francisco, CA, January 7-11, 2006. A31.

25. Sieckman D, Tomori T, Meyerhoff JL, Steinbach T, McCarron R. An experimental model for the study of traumatic brain injury (TBI) combined with hemorrhagic shock (HS). Advanced Technology Applications for Combat Casualty Care, St. Pete Beach, Florida, August 13-17, 2006.

Infectious Diseases Directorate (04)

Publications:

Viral Diseases Department

1. Apt D, Raviprakash K, Brinkman A, Semyonov A, Yang S, Skinner C, Diehl L, Lyons R, Porter K, Punnonen J. Tetravalent neutralizing antibody response against four dengue serotypes by a single chimeric dengue envelope antigen. Vaccine. 2006 Jan 16; 24(3):335-44.

2. Blair PJ, Kochel TJ, Raviprakash K, Guevara C, Salazar M, Wu SJ, Olson JG, Porter KR. Evaluation of immunity and protective efficacy of a dengue-3 premembrane and envelope DNA vaccine in Aotus nancymae monkeys. Vaccine. 2006 Feb 27; 24(9):1427-32.

3. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, Armstrong AW, Fraser S, Wallace MR. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. Journal of Acquired Immune Deficiency Syndromes. 2006 Feb 1; 41(2):194-200.

4. Danko JR, Roberts A. Images in HIV/AIDS. Pruritic cryptococcal skin lesions in an HIV-positive person. AIDS Reader. 2006 Dec; 16(12):660-2.

5. Martin NC, Pardo J, Simmons M, Tjaden JA, Widjaja S, Marovich MA, Sun W, Porter KR, Burgess TH. An immunocytometric assay based on dengue infection via DC-SIGN permits rapid measurement of anti-dengue neutralizing antibodies. Journal of Virological Methods. 2006 Jun; 134(1-2):74-85.

6. Raviprakash K, Apt D, Brinkman A, Skinner C, Yang S, Dawes G, Ewing D, Wu SJ, Bass S, Punnonen J, Porter K. A chimeric tetravalent dengue DNA vaccine elicits neutralizing antibody to all four virus serotypes in rhesus macaques. Virology. 2006 Sep 15; 353(1):166-73.

7. Raviprakash K, Porter KR. Needle-free injection of DNA vaccines: a brief overview and methodology. Methods in Molecular Medicine. 2006; 127:83-9.

8. Simmons M, Porter KR, Hayes CG, Vaughn DW, Putnak R. Characterization of antibody responses to combinations of a dengue virus type 2 DNA vaccine and two

dengue virus type 2 protein vaccines in rhesus macaques. Journal of Virology. 2006 Oct; 80(19):9577-85.

9. Sun P, Celluzzi CM, Marovich M, Subramanian H, Eller M, Widjaja S, Palmer D, Porter K, Sun W, Burgess T. CD40 ligand enhances dengue viral infection of dendritic

cells: a possible mechanism for T cell-mediated immunopathology. Journal of Immunology. 2006 Nov 1; 177(9):6497-503.

10. Suwandono A, Kosasih H, Nurhayati, Kusriastuti R, Harun S, Ma'roef C, Wuryadi S, Herianto B, Yuwono D, Porter KR, Beckett CG, Blair PJ. Four dengue virus serotypes found circulating during an outbreak of dengue fever and dengue haemorrhagic fever in Jakarta, Indonesia, during 2004. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2006 Sep; 100(9):855-62.

Malaria Research Department

1. Ak M, Keles E, Karacasu F, Pektas B, Akkafa F, Ozgur S, Sahinoz S, Ozcirpici B, Bozkurt AI, Sahinoz T, Saka EG, Ceylan A, Ilcin E, Acemioglu H, Palanci Y, Gul K, Akpinar N, Jones TR, Ozcel MA. The distribution of the intestinal parasitic diseases in the Southeast Anatolian (GAP=SEAP) region of Turkey. Parasitology Research. 2006 Jul; 99(2):146-52.

2. Bejon P, Keating S, Mwacharo J, Kai OK, Dunachie S, Walther M, Berthoud T, Lang T, Epstein J, Carucci D, Moris P, Cohen J, Gilbert SC, Peshu N, Marsh K, Hill AV. Early gamma interferon and interleukin-2 responses to vaccination predict the late resting memory in malaria-naive and malaria-exposed individuals. Infection and Immunity. 2006 Nov; 74(11):6331-8.

3. Doolan DL, Martinez-Alier N. Immune response to pre-erythrocytic stages of malaria parasites. Current Molecular Medicine. 2006 Feb; 6(2):169-85.

4. Dunachie SJ, Walther M, Epstein JE, Keating S, Berthoud T, Andrews L, Andersen RF, Bejon P, Goonetilleke N, Poulton I, Webster DP, Butcher G, Watkins K, Sinden RE, Levine GL, Richie TL, Schneider J, Kaslow D, Gilbert SC, Carucci DJ, Hill AV. A DNA prime-modified vaccinia virus ankara boost vaccine encoding thrombospondin-related adhesion protein but not circumsporozoite protein partially protects healthy malaria-naive adults against Plasmodium falciparum sporozoite challenge. Infection and Immunity. 2006 Oct; 74(10):5933-42.

5. Epstein JE, Hoffman SL. Typhoid fever. In: RL Guerrant; DH Walker; PF Weller, editors. Tropical Infectious Diseases: Principles, Pathogens, and Practice. Philadelphia, PA: Elsevier Churchill Livingstone, 2006.

6. Fryauff DJ, Hanafi HA, Klena JD, Hoel DF, Appawu M, Rogers W, Puplampu N, Odoom S, Kweku M, Koram K, Wilson MD, Raczniak G, Boakye D. Short report: ITS-1 DNA sequence confirmation of Leishmania major as a cause of cutaneous leishmaniasis

from an outbreak focus in the Ho district, southeastern Ghana. American Journal of Tropical Medicine and Hygiene. 2006 Sep; 75(3):502-4.

7. Maguire JD, Krisin, Marwoto H, Richie TL, Fryauff DJ, Baird JK. Mefloquine is highly efficacious against chloroquine-resistant Plasmodium vivax malaria and Plasmodium falciparum malaria in Papua, Indonesia. Clinical Infectious Diseases. 2006 Apr 15; 42(8):1067-72.

8. Mlambo G, Mutambu SL, Mduluza T, Soko W, Mbedzi J, Chivenga J, Lanar DE, Singh S, Carucci D, Gemperli A, Kumar N. Antibody responses to Plasmodium falciparum vaccine candidate antigens in three areas distinct with respect to altitude. Acta Tropica. 2006 Nov; 100(1-2):70-8.

9. Sedegah M, Rogers WO, Belmonte A, Belmonte M, Banania G, Patterson N, Ferrari M, Kaslow DC, Carucci DJ, Richie TL, Doolan DL. VaxfectinTM enhances immunogenicity and protective efficacy of P. yoelii circumsporozoite DNA vaccines. Vaccine. 2006 Mar 10; 24(11):1921-7.

10. Sundaresh S, Doolan DL, Hirst S, Mu Y, Unal B, Davies DH, Felgner PL, Baldi P. Identification of humoral immune responses in protein microarrays using DNA microarray data analysis techniques. Bioinformatics. 2006 Jul 15; 22(14):1760-6.

11. Wille-Reece U, Flynn BJ, Lore K, Koup RA, Miles AP, Saul A, Kedl RM, Mattapallil JJ, Weiss WR, Roederer M, Seder RA. Toll-like receptor agonists influence the magnitude and quality of memory T cell responses after prime-boost immunization in nonhuman primates. Journal of Experimental Medicine. 2006 May 15; 203(5):1249-58.

Enteric Diseases Department

1. Bolin I, Wiklund G, Qadri F, Torres O, Bourgeois AL, Savarino S, Svennerholm AM. Enterotoxigenic Escherichia coli with STh and STp genotypes is associated with diarrhea both in children in areas of endemicity and in travelers. Journal of Clinical Microbiology. 2006 Nov; 44(11):3872-7.

2. Carpenter CM, Hall ER, Randall R, McKenzie R, Cassels F, Diaz N, Thomas N, Bedford P, Darsley M, Gewert C, Howard C, Sack RB, Sack DA, Chang HS, Gomes G, Bourgeois AL. Comparison of the antibody in lymphocyte supernatant (ALS) and ELISPOT assays for detection of mucosal immune responses to antigens of enterotoxigenic Escherichia coli in challenged and vaccinated volunteers. Vaccine. 2006 May 1; 24(18):3709-18. Epub 2005 Jul 26.

3. Chen Q, Savarino SJ, Venkatesan MM. Subtractive hybridization and optical mapping of the enterotoxigenic Escherichia coli H10407 chromosome: isolation of unique sequences and demonstration of significant similarity to the chromosome of E. coli K-12. Microbiology. 2006 Apr; 152(Pt 4):1041-54.

4. Goon S, Ewing CP, Lorenzo M, Pattarini D, Majam G, Guerry P. A sigma28-regulated nonflagella gene contributes to virulence of Campylobacter jejuni 81-176. Infection and Immunity. 2006 Jan; 74(1):769-72.

5. Guerry P, Ewing CP, Schirm M, Lorenzo M, Kelly J, Pattarini D, Majam G, Thibault P, Logan S. Changes in flagellin glycosylation affect Campylobacter autoagglutination and virulence. Molecular Microbiology. 2006 Apr; 60(2):299-311.

6. Islam D, Lewis MD, Srijan A, Bodhidatta L, Aksomboon A, Gettayacamin M, Baqar S, Scott D, Mason CJ. Establishment of a non-human primate Campylobacter disease model for the pre-clinical evaluation of Campylobacter vaccine formulations. Vaccine. 2006 May 1; 24(18):3762-71.

7. Jones FR, Baqar S, Gozalo A, Nunez G, Espinoza N, Reyes SM, Salazar M, Meza R, Porter CK, Walz SE. New World monkey Aotus nancymae as a model for Campylobacter jejuni infection and immunity. Infection and Immunity. 2006 Jan; 74(1):790-3.

8. Jones FR, Hall ER, Tribble D, Savarino SJ, Cassels FJ, Porter C, Meza R, Nunez G, Espinoza N, Salazar M, Luckett R, Scott D. The New World primate, Aotus nancymae, as a model for examining the immunogenicity of a prototype enterotoxigenic Escherichia coli subunit vaccine. Vaccine. 2006 May 1; 24(18):3786-92. Epub 2005 Aug 30.

9. Kanipes MI, Papp-Szabo E, Guerry P, Monteiro MA. Mutation of waaC, encoding heptosyltransferase I in Campylobacter jejuni 81-176, affects the structure of both lipooligosaccharide and capsular carbohydrate. Journal of Bacteriology. 2006 May; 188(9):3273-9.

10. Lewis FS, Norton SA, Bradshaw RD, Lapa J, Grabenstein JD. Analysis of cases reported as generalized vaccinia during the US military smallpox vaccination program, December 2002 to December 2004. Journal of the American Academy of Dermatology. 2006 Jul; 55(1):23-31.

11. Li YF, Poole S, Rasulova F, Esser L, Savarino SJ, Xia D. Crystallization and preliminary X-ray diffraction analysis of CfaE, the adhesive subunit of the CFA/I fimbriae from human enterotoxigenic Escherichia coli. Acta Crystallographica Section F, Structural Biology and Crystallization Communications. 2006 Feb 1; 62(Pt 2):121-4.

12. McKenzie R, Bourgeois AL, Engstrom F, Hall E, Chang HS, Gomes JG, Kyle JL, Cassels F, Turner AK, Randall R, Darsley M, Lee C, Bedford P, Shimko J, Sack DA. Comparative safety and immunogenicity of two attenuated enterotoxigenic Escherichia coli vaccine strains in healthy adults. Infection and Immunity. 2006 Feb; 74(2):994-1000.

13. McNally DJ, Hui JP, Aubry AJ, Mui KK, Guerry P, Brisson JR, Logan SM, Soo EC. Functional characterization of the flagellar glycosylation locus in Campylobacter jejuni 81-176 using a focused metabolomics approach. Journal of Biological Chemistry. 2006 Jul 7; 281(27):18489-98.

14. Putnam SD, Sanders JW, Frenck RW, Monteville M, Riddle MS, Rockabrand DM, Sharp TW, Frankart C, Tribble DR. Self-reported description of diarrhea among military populations in operations Iraqi Freedom and Enduring Freedom. Journal of Travel Medicine. 2006 Mar-Apr; 13(2):92-9.

15. Riddle MS, Sanders JW, Putnam SD, Tribble DR. Incidence, etiology, and impact of diarrhea among long-term travelers (US military and similar populations): a systematic review. American Journal of Tropical Medicine and Hygiene. 2006 May; 74(5):891-900.

16. Rockabrand DM, Shaheen HI, Khalil SB, Peruski LF, Jr., Rozmajzl PJ, Savarino SJ, Monteville MR, Frenck RW, Svennerholm AM, Putnam SD, Sanders JW. Enterotoxigenic Escherichia coli colonization factor types collected from 1997 to 2001 in US military personnel during operation Bright Star in northern Egypt. Diagnostic Microbiology and Infectious Disease. 2006 May; 55(1):9-12. Epub 2006 Mar 20.

17. Rotanova TV, Botos I, Melnikov EE, Rasulova F, Gustchina A, Maurizi MR, Wlodawer A. Slicing a protease: structural features of the ATP-dependent Lon proteases gleaned from investigations of isolated domains. Protein Science. 2006 Aug; 15(8):1815-28.

Rickettsial Diseases Department

1. Jiang J, Soeatmadji DW, Henry KM, Ratiwayanto S, Bangs MJ, Richards AL. Rickettsia felis in Xenopsylla cheopis, Java, Indonesia. Emerging Infectious Diseases. 2006 Aug; 12(8):1281-3.

2. Rozmajzl PJ, Houhamdi L, Jiang J, Raoult D, Richards AL. Validation of a Rickettsia prowazekii-specific quantitative real-time PCR cassette and DNA extraction protocols using experimentally infected lice. Annals of the New York Academy of Sciences. 2006 Oct; 1078:617-9.

Presentations:

Viral Diseases Department

1. Beckett C. Update on Avian Influenza. Asian Pacific American Medical Student Association (APAMSA), 13th Annual National Conference, USUHS, Bethesda, MD, October 6-8, 2006.

2. Burgess TH. Experimental dengue viremia and immunogenicity in Yucatan miniature swine: successful development of the first intermediate animal model for dengue virus infection and dengue vaccine testing. Military Health Research Forum, San Juan, Puerto Rico, May 1-4, 2006.

3. Burgess TH, Robinson J, Tjaden JA, Pardo J, Subramanian H, Johnson T, Reed CB, Ewing D, Porter KR, Kochel T. Yucatan Miniature swine develop dengue viremia and are a potential model for dengue immunopathology. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):232.

4. Chen L, Ewing D, Subramanian H, Block K, Rayner J, Porter K, Raviprakash K. A dengue virus vaccine based on alphavirus replicons induces protective immune responses in cynomolgus macaques. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):31-2.

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11. Tjaden JA, Pardo J, Subramanian H, Reed CB, Porter KR, Burgess TH. DNA vaccine encoding dengue premembrane and envelope (PrM/E) induces robust antibody and cellular immune responses in swine: development of a novel large animal model for dengue immunogenicity. 55th Annual Meeting of the American Society for Tropical

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Malaria Research Department

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9. Epstein JE, Rao S, Williams F, Freilich D, Luke T, Sedegah M, de la Vega P, Sacci J, Richie TL, Hoffman SL. (Poster). Safety and clinical outcome of experimental challenge of human volunteers with Plasmodium falciparum infected mosquitoes: an update. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006.

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the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006.

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26. Tamminga C, Chretien JP, Gerena L, Butler W, Milhous W. (Poster) P. falciparum infection among US Marines deployed to Liberia: comparison of mefloquine resistance patterns to archived Liberia isolates and previous studies. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. ORA No. 2006

Enteric Diseases Department

1. Arora R, Baqar S, Tribble D, Lapa J, A., Williams C, Nelson MR. (Oral presentation). Immunologic response after intranasal recombinant flagellin subunit Campylobacter (rFla-MBP) vaccination. 20th Annual Harold S. Nelson Allergy & Immunology Symposium, Miami, FL, March 2, 2006.

2. Hamilton Spence EC, Riley DM, Sparks JW, Lawson JR, Heresi GP, Lin CL, Baqar S, Moya F, Murphy JR. (Poster). Patterns of cytokines in cord blood. Pediatric Academic Societies' Annual Meeting, San Francisco, California, April 29-May 2, 2006. Abstract No. 2851.139.

3. Hickey TE, Poly F, Ewing CP, Goon S, Majam G, Guerry P. Characterization of a secreted protein that is co-regulated with flagella in Campylobacter jejuni. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006.

4. Kanipes MI, Rockabrand D, Guerry P, Akelaitis A, Li J, Monteiro M. Characterization of a Campylobacter jejuni 81-176 two domain glycosyltransferase mutant involved in

lipooligosaccharide biosynthesis. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006. Poster No. 160.

5. Kathirvel E, Lin T, Li X, Chao CC, Ching WM. Phylogenetic analysis of Orientia tsutsugamushi strains based on the protein sequence homologies of 47kDa antigen. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006. Presentation No. D-062.

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7. Perez N, Murphy JR, Baqar S, Yafi M, Heresi GP. Immune reconstitution associated Graves' disease following successful HAART therapy of HIV of an eleven year old.

Pediatric Academic Societies' Annual Meeting, San Francisco, California, April 29-May 2, 2006. Abstract No. 328.

8. Poole S, McVeigh AL, Rasulova F, Brinkley C, O'Dowd A, Savarino SJ. Purification and characterization of recombinant CsbD, the minor subunit of CS17 fimbriae of enterotoxigenic Escherichia coli. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006.

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10. Wu Y, McDaniel J, Thornton S, Osorio M, Kopecko D. Requirements for high-frequency, "adaptive" mutations to stable expression of lactose utilization in Shigella sonnei. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006.

Rickettsial Diseases Department
1. Chao CC, Mutumanje EA, Chen HW, Sun M, Zhang Z, Ching WM. Evaluation of a recombinant fragment of outer membrane protein B from Rickettsia typhi as a diagnostic reagent. USUHS Research Week 2006, Bethesda, MD, May 16-18, 2006.

2. Chen HW, Ching WM. (Poster). Expression, purification and refolding of a 75 kDa fragment AN of the outer membrane protein (OmpB) from Rickettsia typhi. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006.

3. Chen HW, Li X, Ching WM. Reactivity study of scrub typhus patient sera with human serine protease 11 (rhsp11) and Orientia tsutsugamushi outer membrane protein r47b. USUHS Research Week 2006, Bethesda, MD, May 16-18, 2006.

4. Ching WM, Ni YS, Chao CC, Chan TC, Jiang J, Chattopadhyay S, Richards AL. The 47 kDa antigen of Orientia tsutsugamushi Karp strain provided heterologous protection in a mouse lethal challenge model. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):106.

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6. Graf PCF, Richards AL, Manuel KR, Lay J, Nevin R, Gaydos JC, Chretien JP. (Poster). Seroprevalence to Rickettsioses in US military forces deployed to Korea. 55th

Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006.

7. Jiang J, Flyer JG, Fryauff MJ, Klee LM, Chen SC, Miller MK, Stromdahl EY, Rozmajzl PJ, Richards AL. A new protocol for the detection and identification of Rickettsiae in ticks removed from military personnel. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):105.

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9. Pimentel G, Parker T, Fadeel MA, Maksoud MA, Morcos M, El Mofty M, Wasfy M, Jiang J, Richards A, El Sayed N, Hajjeh R. (Poster). Laboratory-based surveillance for acute febrile illness in Egypt: a focus on Rickettsioses. International Conference on Emerging Infectious Diseases, Atlanta, GA, March 19-22, 2006. Presentation No. 311/75.

10. Whitman TJ, Richards AL, Paddock CD, Tamminga CL, Sanders JW. (Poster). Rickettsia parkeri in a US serviceman with a tick bite. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006.

Bone Marrow Research Directorate (05)

Publications:

BONE MARROW PUBS 2006

1. Almeciga I, Wang ZC, Zuniga J, Fernandez-Vina M, Clavijo O, Araujo H, Romero V, Henry J, Ferrone S, Yunis EJ. Allorecognition of an HLA-A*01 aberrant allele by an HLA identical family member carrying the HLA-A*0101 allele. Journal of Immunology. 2006 Dec 15; 177(12):8643-9.

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3. Hurley CK, Wagner JE, Setterholm MI, Confer DL. Advances in HLA: practical implications for selecting adult donors and cord blood units. Biol Blood Marrow Transplant. 2006 Jan; 12(1 Suppl 1):28-33.

4. Lazaro AM, Cao K, Masaberg C, Steiner NK, Xiao Y, Tu B, Turner V, Nickerson P, Stoll S, Schall C, Valdez R, Ng J, Hartzman RJ, Hurley CK. Twenty-three novel HLA-B

alleles identified during intermediate-resolution testing. Tissue Antigens. 2006 Sep; 68(3):245-8.

5. Lazaro AM, Steiner NK, Cao K, Slack R, Chen DS, Xiao Y, Beduhn E, Ng J, Hartzman RJ, Hurley CK. Searching for HLA-DRB1*1206 in volunteer marrow donors in four US population groups. Tissue Antigens. 2006 Nov; 68(5):439-41.

6. Steiner NK, Hurley CK. KIR3DL3 allelic diversity: six new alleles exhibit both conservative and non-conservative substitutions. Tissue Antigens. 2006 Apr; 67(4):277-83.

7. Tang TF, Hou L, Tu B, Hwang WY, Yeoh AE, Ng J, Hurley CK. Identification of nine new HLA class I alleles in volunteers from the Singapore stem cell donor registries. Tissue Antigens. 2006 Dec; 68(6):518-20.

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1. Belle I, Hou L, Chen M, Steiner NK, Ng J, Hurley CK. Investigation of killer cell immunoglobulin-like receptor gene diversity in KIR3DL1. 32nd Annual Meeting of the American Society for Histocompatibility and Immunogenetics, October 16-20, 2006, San Diego, Calif. Human Immunology. 2006; 67(Suppl 1):S97.

2. Hou L, Chen M, Steiner NK, Belle I, Ng J, Hurley CK. Investigation of killer cell immunoglobulin-like receptor gene diversity in KIR2DL1. 32nd Annual Meeting of the American Society for Histocompatibility and Immunogenetics, October 16-20, 2006, San Diego, Calif. Human Immunology. 2006; 67(Suppl 1):S97.

3. Lazaro A, Steiner NK, Cao K, Slack R, Chen S, Xiao Y, Beduhn E, Ng J, Hartzman RJ, Hurley CK. Seeking DRB1*1206 in four U.S. population groups. 32nd Annual Meeting of the American Society for Histocompatibility and Immunogenetics, October 16-20, 2006, San Diego, Calif. Human Immunology. 2006; 67(Suppl 1):S157.

Biologic Defense Research Directorate (06)

Publications:

1. Dean D, Myers GS, Read TD. Lessons and challenges arising from the "first wave" of chlamydial genomics. In: P Bavoil; P Wyrick, editors. Chlamydia: Genomics and Pathogenesis. Wymondham: Horizon Bioscience, 2006.

2. Fouts DE, Rasko DA, Cer RZ, Jiang L, Fedorova NB, Shvartsbeyn A, Vamathevan JJ, Tallon L, Althoff R, Arbogast TS, Fadrosh DW, Read TD, Gill SR. Sequencing

Bacillus anthracis typing phages gamma and cherry reveals a common ancestry. Journal of Bacteriology. 2006 May; 188(9):3402-8.

3. Krishnamurthy T, Hewel J, Bonzagni NJ, Dabbs J, Bull RL, Yates JR, 3rd. Simultaneous identification and verification of Bacillus anthracis. Rapid Communications in Mass Spectrometry: RCM. 2006; 20(13):2053-6.

4. Raines KW, Kang TJ, Hibbs S, Cao GL, Weaver J, Tsai P, Baillie L, Cross AS, Rosen GM. Importance of nitric oxide synthase in the control of infection by Bacillus anthracis. Infection and Immunity. 2006 Apr; 74(4):2268-76.

5. Read TD, Ussery DW. Opening the pan-genomics box. Current Opinion in Microbiology. 2006 Oct; 9(5):496-8.

6. Sozhamannan S, Chute MD, McAfee FD, Fouts DE, Akmal A, Galloway DR, Mateczun A, Baillie LW, Read TD. The Bacillus anthracis chromosome contains four conserved, excision-proficient, putative prophages. BMC Microbiol. 2006; 6:34.

7. Thomason B, Read TD. Shuffling bacterial metabolomes. Genome Biology. 2006 Feb; 7(2):204. Epub 2006 Feb 27.

Presentations:

1. Baillie L. (Oral presentation). Biodefense Defense Research Directorate. DTRA Country Science Workshop, Kazakhstan, May 14, 2006.

2. Bedwell DW, Wolcott MJ, Newell SW, Carpenter J, Chuvala LJ, Scherer JM. Identification and differentiating of Francisella tularensis by automated ribotyping. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006.

3. Clark JL, Lescano AG, Konda KA, Kegeles S, Leon SR, Jones FR, Klausner JD, Caceres CF, Coates TJ, NIMH Collaborative HIV/STD Prevention Trial Group. (Poster). Frequency and associated characteristics of male sexual conduct in Peruvian low-income urban males. XVI International AIDS Conference (AIDS 2006), Toronto, Canada, August 13-18, 2006. IAS Abstract Archive. Abstract no. CDD0328.

4. Jones F. Opportunities in government. 106th General Meeting of the American Society for Microbiology, Orlando, FL, May 21-25, 2006.

5. Kang TJ, Chen WH, Basu S, Fenton MJ, Weiner MA, Hibbs S, Baillie L, Cross AS. Critical role for caspase-1 in the innate immune response to Bacillus anthracis. Immunology 2006: Annual Meeting of the American Association of Immunologists, Boston, Massachusetts, May 12-16, 2006. Journal of Immunology. 2006 Apr 1; 176(7 Suppl):S98-9.

6. Konda KA, Leon SR, Lescano AG, Klausner JD, Meza R, Jones FR, Caceres CF, Coates TJ, NIMH Collaborative HIV/STD Prevention Trial Group. The epidemiology of syphilis cases in three socially marginalized populations of low-income, urban, coastal

Peru. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):14.

7. Konda KA, Sandoval C, Lescano AG, Giron JM, Salazar X, Jones FR, Coates TJ, Caceres CF, NIMH Collaborative HIV/STD Prevention Trial Group. The characteristics, risk behaviors and STI prevalences among socially marginalized women in low-income urban, coastal Peru. 55th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Atlanta, GA, November 12-16, 2006. American Journal of Tropical Medicine and Hygiene. 2006 Nov; 75(5 Suppl):41.

8. Lescano AG, Clark JL, Konda KA, Kegeles S, Jones FR, Caceres CF, Coates TJ, NIMH Collaborative HIV/STD Prevention Trial Group. Alcohol use prior to sex and its association with risk behavior among socially marginalized, low-income populations in Peru. XVI International AIDS Conference (AIDS 2006), Toronto, Canada, August 13-18, 2006. IAS Abstract Archive. Abstract no. CDD0582.

9. Lescano AG, Konda KA, Clark JL, Galea J, Klausner JD, Jones FR, Leon SR, Caceres CF, Coates TJ, NIMH Collaborative HIV/STD Prevention Trial Group. (Poster). Recent onset of STI symptoms, actions to prevent transmission and symptom management in low-income, socially marginalized populations in urban, coastal Peru. XVI International AIDS Conference (AIDS 2006), Toronto, Canada, August 13-18, 2006. IAS Abstract Archive. Abstract no. TUPE0411.

10. Pomerantseva O, Pomerantsev A, Leppla S, Baillie L. Evidence for contribution of Bacillus cereus PLCR-PAPR quorum-sensing system to activation of Bacullus anthracis secretome. National Conference on Gram-Positive Pathogens, Omaha, NE, October 15-18, 2006.

11. Read T. Population genomics of Bacillus anthracis and close relatives. University of Maryland Biotechnology Institute Faculty Retreat, April 5, 2006.

12. Read TD. Population genomics of Bacillus anthracis and close relatives. Naval Research Laboratory, Washington, DC, March 30, 2006.

13. Read TD. Genomics of Bacillus anthracis and close neighbors. Defence Science & Technology Laboratory, Porton Down, Salisbury, UK, April 10, 2006.

14. Sozhamannan S. (Course). Biodefense Laboratory Methods. Johns Hopkins University, 2006.

15. Sozhamannan S. (Guest Speaker). Bacteriophage therapy - application of an old idea to new problems in biodefense. National Insitute of Standards and Technology, Gaithersburg, MD, March 23, 2006.

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## 6. Photographs

List below official photographs and any other command-generated media being submitted in either electronic or paper format. Photographs to be submitted include: official photo of commanding officer; recent photo of ship, aircraft, or facility; and photos of historic events associated with the command. Photographs submitted electronically should be in JPG, TIFF or GIF format. It is unnecessary to convert non-electronic documents to electronic format. Photographs in electronic format are to be submitted via e-mail or on CD-ROM as explained below. Enclosures that do not exist in electronic format should be listed below and submitted in the same manner as the CD-ROM. Also include any photographs covering operational strikes, battle damage (especially that sustained by own ship, aircraft, facilities or equipment), or other relevant photos relating to combat or deployment operations.

Attachment (4) Photograph of the Commanding Officer (.pdf format)
Attachment (5) Photograph of the Executive Officer (.pdf format)

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